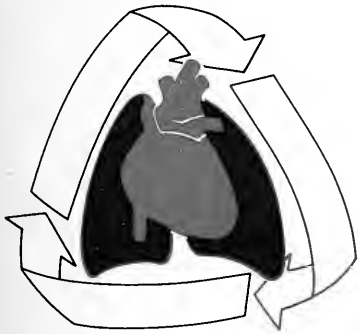
NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM



FOURTH
REPORT
OF THE
DIRECTOR
OF THE
NATIONAL HEART,
LUNG, AND BLOOD
INSTITUTE

U.S DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE

Public Health Service
National Institutes of Health

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MARCH 1, 1977

U.S. DEPARTMENT OF HEALTH,
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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

March 1, 1977

The President
The White House
Washington, D.C.

Dear Mr. President:

I am pleased to submit to you for transmittal to the Congress the Fourth Report of the Director of the National Heart, Lung, and Blood Institute.

The National Heart, Blood Vessel, Lung, and Blood Program is aimed at diseases that annually account for more than half of the deaths and about one-third of the economic costs of all diseases in the United States. Thirty million Americans suffer from heart, blood vessel, lung and blood diseases, and one million die from them each year. The annual economic cost of these diseases is over 60 billion dollars. The emotional and social losses are immeasurable.

The Program is achieving important results. The death rate from cardiovascular diseases has shown a decline of 30 percent since 1950 compared to a decline in noncardiovascular diseases of 18 percent. Since 1970, this decline has accelerated, dropping 14 percent--more than twice that of noncardiovascular diseases. This large decline in cardiovascular disease deaths may be due to many factors including changes in diet, exercise, smoking, emergency medical facilities, and hypertension awareness, as well as other causes we do not yet understand. The Institute is actively pursuing this question through epidemiologic studies and an extensive program of clinical trials.

The progress in the fight against these diseases is a tribute to the imagination and dedication of the people who have guided and conducted the research programs of the Institute. This report is submitted with a sense of pride in those who have made the report possible.

Sincerely,

Robert Levy

Robert I. Levy, M.D.
Director

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ABBREVIATIONS

ABC	American Blood Commission
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
AHA	American Heart Association
AMA	American Medical Association
AMIS	Aspirin Myocardial Infarction Study
BCHS	Bureau of Community Health Services
BEIRS	Blood Establishment Information and Registration System
BID	bureau, institute, division
BoB	Bureau of Biologics
BQA	Bureau of Quality Assurance
BURP	bubble ultrasonic resonance pressure
CAST	Coronary Artery Surgery Trial
CDC	Center for Disease Control
CDS	Community Development Services
CHD	coronary heart disease
CHS	Community Health Services
CKP-MB	creatinine phosphokinase
CO	carbon monoxide
COLD(s)	chronic obstructive lung disease(s)
CPAP	constant positive airway pressure
CPPT	Coronary Primary Prevention Trial
CVD	cardiovascular disease
DBDR	Division of Blood Diseases and Resources
DHEW	Department of Health, Education, and Welfare
DHVD	Division of Heart and Vascular Diseases
DLD	Division of Lung Diseases
DOD	Department of Defense
DOT	Department of Transportation
2,3-DPG	2,3-disphosphoglycerate
EKG	electrocardiogram
EMOS	Extracorporeal Membrane Oxygenator Study
EPA	Environmental Protection Agency
ERDA	Energy Research and Development Administration
FDA	Food and Drug Administration
FRG	Federal Republic of Germany
HBIG	Hepatitis B immune globulin
HBP	high blood pressure
HDFP	Hypertension Detection and Follow-up Program
HDL	high-density lipoprotein
HLA	histocompatibility antigen
HRA	Health Resources Administration
HSA	Health Services Administration
IATC	Interagency Technical Committee
ICTH	International Committee on Thrombosis and Hemostasis
IHD	ischemic heart disease

IPPB	intermittent positive pressure breathing
IRG	Investigator-Initiated Research Grant
LDL	low-density lipoprotein
LRCP	Lipid Research Clinic Program
LRCs	Lipid Research Clinics
LRCs-CPPT	Lipid Research Clinics-Coronary Primary Prevention Trial
MIRUs	Myocardial Infarction Research Units
MRFIT	Multiple Risk Factor Intervention Trial
NASA	National Aeronautics and Space Administration
NCC	Nutrition Coding Center
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NHBPEP	National High Blood Pressure Education Program
NHBPERP	National High Blood Pressure Education Research Program
NHF	National Hemophilia Foundation
NHLI	National Heart and Lung Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIAMDD	National Institute of Arthritis, Metabolism, and Digestive Diseases
NIH	National Institutes of Health
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NRDC	National Research and Demonstration Center
NRDS	Neonatal Respiratory Distress Syndrome
NRSA	National Research Service Award
NSF	National Science Foundation
OPEC	Office of Prevention, Education, and Control
PAA	Pulmonary Academic Award
PECP	Prevention, Education, and Control Program
PSROs	Professional Standards Review Organizations
RCDA	Research Career Development Award
RDS	Respiratory Disease Syndrome
RFA	Request for Applications
SAM	surface-active material
SCORs	Specialized Centers of Research
SRS	Social and Rehabilitation Service
SSA	Social Security Administration
TWG	Tobacco Working Group
USAF	US Air Force
USDA	US Department of Agriculture
VA	Veterans Administration
VHCC	Viral Hepatitis Coordinating Committee

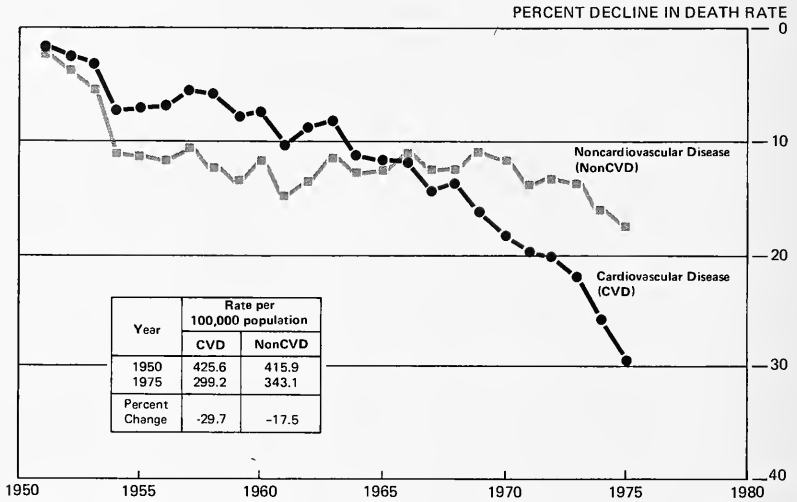
I.
INTRODUCTION

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 issued a mandate to marshall the nation's health resources in a comprehensive National Program to prevent and treat cardiovascular, pulmonary, and blood diseases, and to improve utilization of national blood resources. The legislation designated the National Heart and Lung Institute (NHLI), now known as the National Heart, Lung, and Blood Institute (NHLBI), to plan and lead a coordinated attack on these diseases by developing and implementing a national program of research, prevention, education, and control efforts. The status and progress of the resulting National Heart, Blood Vessel, Lung, and Blood Program are presented in this report.

This introductory chapter includes a summary of the magnitude of heart, lung, and blood disease problems. The summary is followed by a brief review of the origin and history of the National Program dating from its inception with the National Heart Act in 1948 to the present, as well as a review and evaluation of the major activities of the Institute during this period. Highlights of recent National Program accomplishments are presented in Chapter II, and a review of the resources required to implement and conduct the planned program is provided in Chapter III. Chapter IV provides a description of the goals, current status, recent progress, and planned actions in each of the 20 major program areas included in the National Program. A similar discussion of recent, current, and planned activities under the Prevention, Education, and Control Program is included in Chapter V. Numerous examples of interagency, federal and nonfederal, and international collaborative studies related to the National Program are outlined in Chapter VI. The education and training programs and awards available to individuals and institutions and needed to sustain the National Plan are described in Chapter VII.

MAGNITUDE OF THE PROBLEM

For more than 50 years, heart and blood vessel diseases have been the major cause of death in this country. In 1975, they accounted for over 50 percent of all deaths annually; nearly three times the death rate from cancer, the next highest cause. Cardiovascular diseases cause two-thirds of all deaths among people over 65 years of age and approximately 160,000 deaths in individuals below age 65. An estimated 30 million persons in the United States have diseases of the heart and blood vessels; this results in a huge burden of acute and chronic illness and disability. Some 27 million of these victims of cardiovascular disorders suffer from hypertension, 4 million from coronary heart disease, and 1.8 million from rheumatic heart disease. Approximately eight out of every one thousand children are born with congenital heart disease and half of these do not survive to their first birthday. However, as indicated in Figure 1, the number of persons in the United States dying from these diseases is decreasing. Since 1950, there has been a 29.7 percent decline in the cardiovascular death rate (age adjusted) compared with a 17.5 percent decline in noncardiovascular deaths (age adjusted). From 1970 to 1975, the deaths due to cardiovascular disease have declined 13.6 percent--more than twice the



Year	Rate per 100,000 population	
	CVD	NonCVD
1950	425.6	415.9
1975	299.2	343.1
Percent Change	-29.7	-17.5

*Age adjusted to United States population in 1940.

Figure 1. **PERCENT DECLINE IN DEATH RATES* SINCE 1950 FOR CARDIOVASCULAR AND NONCARDIOVASCULAR DISEASES (UNITED STATES)**

decline for noncardiovascular diseases. In 1975, the number of deaths from major cardiovascular disease dropped below one million for the first time since 1967 although the population in the United States has increased and is comprised of a larger proportion of senior citizens. Despite such progress, major cardiovascular disease still leads all other causes of death in the United States, with more than 640,000 persons having been predicted to die of coronary heart disease alone in 1976.

Diseases of the lung also constitute a major health problem, a problem that is of increasing dimensions for some of these disorders. Lung diseases account for more than 112,000 deaths annually. Figure 2 summarizes recent data available on chronic lung diseases; these data suggest a continuous increase in the death rate from chronic bronchitis and emphysema. Almost exclusively limited to premature births, respiratory distress syndrome of the neonate accounts for approximately 12,000 deaths annually.

Problems of the blood are intimately related to cardiovascular and pulmonary diseases. The impact of clotting and bleeding disorders is considerable. Arterial thrombosis causes or complicates a variety of serious disorders in all parts of the body. Thrombosis may cause pulmonary embolism--a disorder responsible for the hospitalization of about 200,000 persons annually, approximately

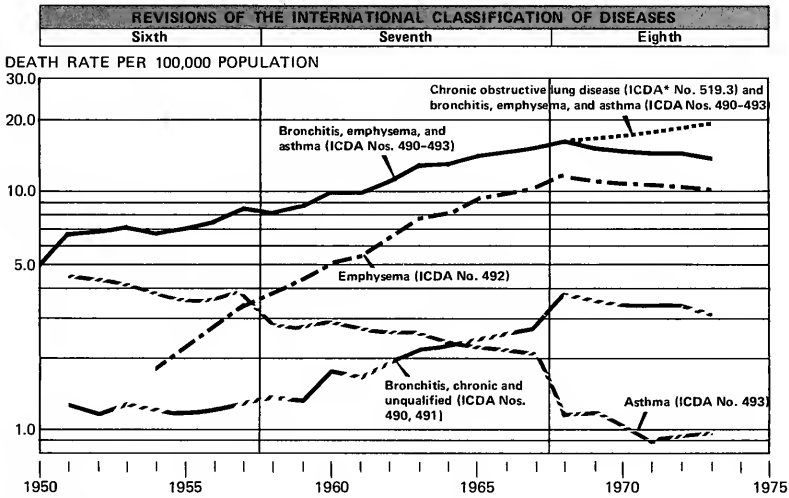


Figure 2. DEATH RATES FOR BRONCHITIS, EMPHYSEMA, ASTHMA, AND OTHER CHRONIC OBSTRUCTIVE LUNG DISEASES, 1950-73

one-third of whom die. Hereditary diseases of the blood constitute a major national health problem. Approximately 2 million persons in the United States, primarily black, carry the sickle cell trait. About one in every four hundred black babies is born with sickle cell anemia. Twenty-five thousand persons in the United States suffer from hemophilia.

Thus, in the United States, diseases of the heart, lung, and blood constitute a major portion of the morbidity and mortality due to physical disorders. Table 1 lists the ten leading causes of death in the United States during 1974. The four disease categories falling within the Institute's mandate are highlighted among the ten causes listed.

Table 1. **TEN LEADING CAUSES OF DEATH IN THE UNITED STATES, 1974**

Cause of Death	Number of Deaths	Percentage of Deaths[1]	Rate per 100,000 Population
Total	1,934,388	100.0	915.1
1. Diseases of the heart	738,171	38.2	349.2
2. Malignant neoplasms	360,472	18.4	170.5
3. Cerebrovascular diseases	207,424	10.7	98.1
4. Accidents	104,622	5.4	49.5
5. Influenza and pneumonia	54,777	2.8	25.9
6. Chronic obstructive lung disease[2]	39,303	2.0	18.6
7. Diabetes mellitus	37,329	1.9	17.7
8. Cirrhosis of the liver	33,319	1.7	15.8
9. Arteriosclerosis	32,239	1.7	15.3
10. Certain causes of early infancy deaths	28,786	1.5	13.6
All other causes	297,946	15.4	141.0

[1]Percentages do not total 100 due to rounding.

[2]This includes deaths from emphysema, bronchitis, and chronic obstructive lung disease. This grouping is not on the official National Center for Health Statistics (NCHS) list of 10 leading causes, but it will be beginning in 1979. The total shown does not reflect deaths from related diseases—asthma and bronchiectasis—that bring total deaths to 41,942.

SOURCE: *Monthly Vital Statistics Report,* Vol. 24, No. 11, US Department of Health, Education, and Welfare, the National Center for Health Statistics, 1976.

Although recent statistics suggest that the morbidity and mortality from some of these diseases are decreasing, the economic losses attributed to cardiovascular, lung, and blood diseases are staggering. In 1972, their estimated cost to the American public was $57 billion as shown in Table 2. Estimated costs for 1974 increased to more than $63 billion: $43.5 billion for cardiovascular disease, $18.6 billion for lung diseases, and $1.1 billion for blood diseases.

Table 2. TOTAL ECONOMIC COST,* 1972
(Amount and Percentage of Distribution)

Diagnosis	Amount ($ Million)				Percentage Distribution			
	Total	Direct Costs	Indirect Costs		Total	Direct Costs	Indirect Costs	
			Morbidity	Mortality			Morbidity	Mortality
Infective and parasitic diseases	$ 3,443	$ 1,412	$ 1,200	$ 831	1.8	1.9	2.8	1.2
Neoplasms	17,367	3,872	862	12,633	9.2	5.1	2.0	17.7
Endocrine, nutritional, and metabolic diseases	5,930	3,436	1,137	1,357	3.1	4.6	2.7	1.9
[redacted]								
Mental disorders	13,917	6,985	6,179	753	7.4	9.3	14.6	1.1
Diseases of the nervous system and sense organs	10,951	5,947	3,944	1,060	5.8	7.9	9.3	1.5
[redacted]								
[redacted]								
Diseases of the digestive system	17,487	11,100	2,606	3,781	9.3	14.8	6.2	5.3
Diseases of the genitourinary system	6,456	4,471	1,249	736	3.4	5.9	3.0	1.0
Complications of pregnancy, childbirth, and the puerperium	2,932	2,607	245	80	1.6	3.5	0.6	0.1
Diseases of the skin and subcutaneous tissue	2,052	1,525	460	67	1.1	2.0	1.1	0.1
Diseases of the musculoskeletal system and connective tissue	8,948	3,636	5,103	209	4.7	4.8	12.1	0.3
Congenital anomalies	1,903	381	238	1,284	1.0	0.5	0.6	1.8
Accidents, poisonings, and violence	26,678	5,121	3,883	17,674	14.1	6.8	9.2	24.8
Other	13,294	7,398	1,494	4,402	7.0	9.8	3.6	6.2
Total	$188,789	$75,231	$42,323	$71,235	100.0%	100.0%	100.0%	100.0%

* Estimated diract expenditures, indirect costs of morbidity and present value of lifatima earings discounted at 4 percent, by diagnosis.

SOURCE: "The Economic Cost of Illnass Ravisited," Barbara S. Cooper and Dorothy P. Rice, Office of Research and Statistics, Social Security Administration, Presented at American Public Health Association Meetings, Chicago, Ill., Nov. 20, 1975.

NATIONAL PROGRAM ORIGIN AND HISTORY

In June 1948, President Truman signed the National Heart Act, establishing the National Heart Institute and assigning it primary responsibility for federal programs in the cardiovascular disease field. In 1969, the Institute was redesignated the National Heart and Lung Institute and was assigned additional responsibilities for research and training activities directed against lung disorders with the exception of cancer and acute infections of the lung. Then in September 1972, the National Heart, Blood Vessel, Lung, and Blood Act enlarged the authority of the Institute and provided for expanded, intensified, and coordinated efforts against heart, blood vessel, lung, and blood diseases. The lung and blood programs were enlarged to include diseases of children such as asthma, cystic fibrosis, hyaline membrane diseases, and hemolytic and hemophilic diseases. Heart, blood vessel, lung, and blood prevention, control and education programs were initiated, and research and demonstration centers were established for heart, blood vessel, lung, and blood diseases in both adults and children. Moreover, the law required that not less than 15 percent of the Institute budget be reserved for diseases of the lung and 15 percent for diseases of the blood. Anticipating the Act which became law in September 1972, the Institute was authorized to reorganize along programmatic lines consonant with the intent of the legislation. In July 1972, the Division of Lung Diseases and the Division of Blood Diseases were established.

The 1972 Act called upon the Director of what was then the National Heart and Lung Institute, with the advice of the National Heart, Lung, and Blood Advisory Council, to develop a plan for a National Program to expand, intensify, and coordinate activities in an accelerated attack against problems involving heart, blood vessel, lung, blood diseases, and blood resources. The National Program developed by the National Heart and Lung Institute and its advisors includes planning, the implementation of many new research programs, and the development of prevention, education, and control programs of relevance to both medical professionals and the public. The Program, which is reviewed annually by the Congress, has four interrelated goals: (1) to promote health, (2) to prevent disease, (3) to treat disease, and (4) to restore health. The Program has been developed and pursued with these goals in mind. The principal components of the broad program strategy are outlined in Figure 3.

On April 22, 1976, the President signed a new bill (PL 94-278) extending the authority of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 for two fiscal years, but with substantive changes. The principal changes involved a series of amendments designed to provide increased emphasis on programs in blood research and in the management of our blood resource. The 1976 Act legislated a change in the name of the National Heart and Lung Institute to the National Heart, Lung, and Blood Institute, and made a comparable change in the name of the Institute's Advisory Council. Thus, the recent legislation has specifically designated the NHLBI as the focal point for studies and research into the science and management of the Nation's blood resources.

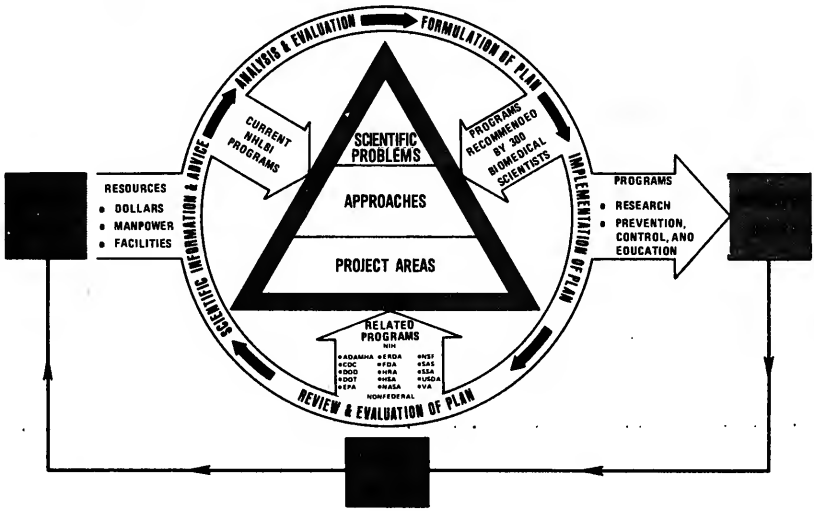


Figure 3. NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM STRATEGY

Under the new 1976 legislation the primary missions of the Institute are to:

- Conduct and support research to increase fundamental and clinical knowledge about the cardiovascular, pulmonary, and blood systems and blood resources
- Develop new or improved techniques for the prevention, diagnosis, and relief of diseases affecting these systems
- Carry out clinical testing and evaluation of new knowledge showing promise in the solution of problems posed by these diseases
- Encourage the application of proven techniques by the medical and research communities

- Support the training of research workers, clinicians, scientists, and teachers in the cardiovascular, blood, and pulmonary fields

- Keep both the general public and health professionals fully informed about research and clinical advances developing out of Institute programs through a comprehensive program involving education and demonstration activities.

TWENTY-FIVE YEARS OF INSTITUTE ACTIVITY

It is difficult to assess program activities and research results during the first year or two after initiation of a large, comprehensive program. However, time now allows the Institute to assess, in a dispassionate way, the first 25 years of heart research since the inception of the National Heart Act in 1948. A few representative advances brought to the American public during this period are reviewed below.

Congential Heart Disease

In 1950, as today, there were 38 recognized types of congenital heart defects. But in 1950 only a few of these defects of the simplest types were correctable. Surgeons attempting to correct serious congenital defects worked quickly and with limited knowledge, guided mainly by the empirical results of previous similar surgical efforts in an operative field that twisted and turned with each heartbeat. They had few priceless seconds in which to accomplish a miracle, and the mortality rate was appalling. In 1953, a prototype heart-lung machine had its earliest trials. Now the heart-lung machine is routinely available and circulation can be supported. With this machine, surgeons can work for hours, if necessary, on stilled hearts. With hypothermia to cool the metabolism of the body and better life-support systems, multiple and complex heart defects can be ameliorated or corrected, and nearly all congenital heart defects now are correctable or can be palliated. The risks are decreasing each year even with the most complex multiple defects in infants and young children.

Rheumatic Heart Disease

In 1950, the relationship of rheumatic heart disease to rheumatic fever and to antecedent streptococcal infections had already been recognized. A new antibiotic--penicillin--was already being used to prevent rheumatic fever and rheumatic heart disease. However, once rheumatic heart disease was diagnosed in a patient, the outcome was grave. Valvular defects occurred and progressed, and surgeons who tried to repair stenosed valves often produced incompetent valves and death. The first artificial heart valve was introduced more than 20 years ago. Today, such valves are readily available and multiple valves can be replaced successfully.

Hypertension

In 1950, the prognosis for hypertension was not a happy one; many individuals were diagnosed as having severe hypertension only after end organ damage had

occurred. There was no effective drug therapy, and the drugs which were available had serious side effects. In the 1950's new drugs were introduced. Perhaps the most exciting of these--the thiazide diuretics--were introduced to rid the body of extra salt and water. Now, not only can high blood pressure be controlled, but there is also strong evidence that control of high blood pressure reduces the risk of developing heart failure, renal failure, and stroke.

Coronary Heart Disease

Striking advances of major significance have been made through research and the acquisition of new knowledge in the area of coronary heart disease since 1950; these advances can be measured and evaluated. In 1950, over 700,000 deaths occurred from cardiovascular disease, the major component being coronary heart disease. If the coronary heart disease patient reached the hospital, he would be placed in a regular ward. Therapy was based on the concept of palliative medication and prolonged bed rest. Now with the development of the concept of the acute coronary care unit, irregular heart rhythms and heart rates can be readily controlled. While other factors may also be involved, hospital mortality following acute myocardial infarction (heart attacks) has declined by almost 50 percent since the advent of coronary care units.

Special coronary care units now exist for the benefit of the patient with coronary artery disease. Drugs and resuscitative equipment that were not even conceived of in 1950 are now available. Today it is known that the amount of heart muscle damage that occurs at the time of a heart attack is not fixed when the patient first has pain or is admitted to the hospital. There is a period of perhaps 12 to 72 hours after a heart attack during which time the amount of heart muscle that will die can be influenced. The extent of heart muscle damage can be measured by determining the level of certain enzymes in the blood and by utilizing radioisotopic or electrocardiographic techniques. The amount of heart muscle damage can be decreased, and the heart failure that often occurs after one or more heart attacks can be minimized. Equally important, diseased blood vessels that supply blood to the heart itself can now be bypassed and the circulation restored. Thus, patients with severe chest pain due to insufficient supply of blood to the heart can now be treated and resume productive lives.

INSTITUTE ACTIVITIES SINCE THE 1972 ACT

Evaluation of the four-year period since the passage of the National Heart, Blood Vessel, Lung, and Blood Act is more difficult than the evaluation of the preceding 25 years. In 1976, the Institute initiated a program to examine the progress achieved in the 20 program elements currently included in the National Plan (Table 3).

The Institute utilized the advice and guidance of the National Heart, Lung, and Blood Advisory Council; the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources (IATC); and six technical advisory committees to carry out this review (Table 4). The combined membership of these Committees provided the the necessary scientific expertise to conduct an in-depth review of the Institute's programs.

Table 3. **NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM**

HEART AND BLOOD VESSEL DISEASE	LUNG DISEASE	BLOOD DISEASE AND BLOOD RESOURCES
Arteriosclerosis	Structure and Function of the Lung	Bleeding and Clotting Disorders
Hypertension	Emphysema and Chronic Bronchitis	Disorders of the Red Blood Cell
Cerebrovascular Disease	Pediatric Pulmonary Diseases	Sickle Cell Disease
Coronary Heart Disease	Fibrotic and Immunologic Lung Diseases	Blood Resources
Peripheral Vascular Diseases	Respiratory Failure	
Arryhthmias	Pulmonary Vascular Diseases	
Heart Failure and Shock		
Congenital and Rheumatic Heart Diseases		
Cardiomyopathies and Infections of the Heart		
Circulatory Assistance		

Table 4. **NHLBI COMMITTEES ASSISTING IN THE REEVALUATION OF THE NATIONAL PROGRAM AND THE NATIONAL PLAN**

Arteriosclerosis and Hypertension Advisory Committee
Blood Diseases and Resources Advisory Committee
Cardiology Advisory Committee
Lipid Metabolism Advisory Committee
Pulmonary Diseases Advisory Committee
Clinical Applications and Prevention Advisory Committee

The results of the advisory committee program reviews have provided input material for many parts of this fourth report of the Director of the NHLBI. Below are brief discussions of recent activities in each of four important program areas: (1) Lung Cell Biology, (2) Blood Safety, (3) High Blood Pressure Education, and (4) Prevention.

Lung Cell Biology

In 1970, the Institute initiated a lung program on the premise that expansion of our present knowledge of the structure and function of the normal lung and the modifications that result in disease is essential to any advances in the diagnosis, treatment, or prevention of lung disorders. By drawing upon such basic disciplines as molecular biology, biochemistry, endocrinology, immunology and cell biology, investigations of lung structure and function contribute to understanding the causes (etiology) and the processes that affect the course (pathogenesis) of lung diseases.

It is no longer sufficient to view lung function solely in terms of gas exchange. Increasingly, important aspects of pulmonary function are being traced to biochemical processes in the more than 40 types of cells that comprise the lung and that reflect the diversity of its metabolic activities. Considerable progress has been made in establishing specific functions for some of these cell types, particularly the epithelial cells (Type I and Type II) of the alveoli (air sacs) and the alveolar macrophage which plays a major role in lung defense mechanisms.

It is now known that the alveolar Type I cell displays minimal enzymatic activity and is biochemically specialized to consume little oxygen. However, this metabolically inactive cell is anatomically specialized to provide a very thin barrier to diffusion of oxygen and carbon dioxide between the lung and the capillaries, facilitating gas exchange. On the other hand, the Type II cell is metabolically active and is now believed to have an essential role in secretion of the surface-active material (surfactant) of the lung, a substance that is deficient in neonatal respiratory distress syndrome (hyaline membrane disease).

Over the past few years, studies on lung maturation and surface-active material have led to the development of methods for identifying neonatal respiratory distress syndrome (NRDS). Improved understanding of lung development, including the implications of the presence of surface-active material, has created opportunities for further initiatives in NRDS. Extensive studies on animal models of NRDS have demonstrated that antenatal administration of steroids accelerates lung maturation and significantly diminishes the occurrence of NRDS. A cooperative study was initiated to (1) establish a randomized, double-blind, controlled trial of the effect of corticosteroids administered 24 to 72 hours before parturition on the incidence of NRDS, and (2) to determine whether the therapy has any adverse short-term or long-term effects on the infant.

Blood Safety

Viral hepatitis is the most common infection transmitted by blood and blood products and may be regarded as the most frequent transfusion complication.

After many years of effort, a test for hepatitis B virus is available and is being utilized extensively today in donor screening. While the test is not totally effective, its use has markedly diminished the incidence of hepatitis B virus infections associated with blood transfusion. However, transfusion-associated hepatitis is still a problem which must continue to be viewed in a broader context. A close examination of the blood of recipients indicates an occurrence of posttransfusion hepatitis as high as 12 percent. The great majority of these infections are "subclinical" and are caused by agents other than the hepatitis B virus.

Epidemiologic studies of the transmission of hepatitis B virus and the circumstances under which the carrier state ensued have shown that oral spread is a significant method of transmission. Of additional interest, genetic factors appear to contribute toward the propensity to the carrier state. By testing plasma donations for hepatitis B surface antibody, it has become possible to prepare a specific hyperimmune globulin (hepatitis B immune globulin, or HBIG). The NHLBI sponsored four studies intended to evaluate the prophylactic and treatment potential of this material. These studies include the use of HBIG in the preexposure prophylaxis of transfusion-transmitted disease, in postexposure prophylaxis of medical and laboratory personnel accidentially exposed, and in therapeutic intervention during fulminant Type B disease.

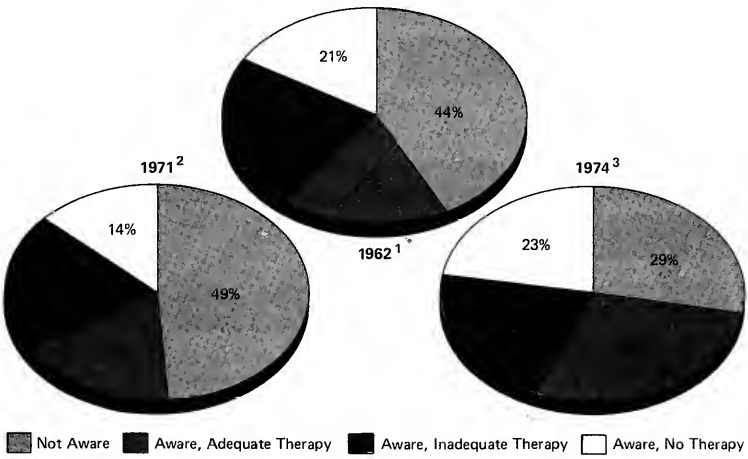
A major new effort, initiated in 1974, is a cooperative prospective study of transfusion-associated hepatitis. Five major medical centers are carrying out follow-up of low-volume recipients. Present and newly proposed tests for detection of carriers among the donors are routinely applied as are available tests for etiologic diagnosis among the recipients. To date many cases of hepatitis are classifiable as "non-A, non-B disease." A unique feature of the study is the storage at the NHLBI of aliquots of all sera collected to be maintained as a "bank" of material for future research and to permit the immediate study of new tests as they become available.

High Blood Pressure Education

The National High Blood Pressure Education Program was established in 1972. The mission of this continuing program is to reduce deaths and illness due to uncontrolled hypertension through education of the public and health professionals.

The need for this effort arises from two conflicting facts: (1) Uncontrolled hypertension leads to increased risk of heart disease, stroke, and kidney failures; however, existing therapy can lower blood pressure with proven reduction of risk. (2) Despite this knowledge, the public was unaware of the dangers and prevalence of high blood pressure, and health professionals were not fully employing available therapies.

Surveys conducted in 1962 and 1971 suggest that little progress was being made in the area of hypertension and control (See Figure 4). The results of these surveys indicate that nearly half of those afflicted with high blood pressure did not know it. About one-fifth did know but were not under therapy, while about another one-fifth were under therapy but not controlled; only about one-sixth were well controlled. However, in 1973 to 1974, after the National High Blood Pressure Education Program had begun, an NHLBI survey in 14 communities suggested that awareness to the disease had climbed; only 29 percent of people with high blood pressure were unaware, while the number well controlled nearly doubled, rising to 29 percent. While the new survey data are not directly comparable with previous national surveys, the differences are of such magnitude as to suggest that the High Blood Pressure Education Program has produced a positive effect on the national attitude toward high blood pressure detection and control. The challenge in this area remains to improve the situation for those under treatment but not controlled, and for those aware of their elevated blood pressure but not being treated.



[1]Health Examination Survey 1960-62. Computed from data published in *Vital and Health Statistics,* Series 2, No. 22, March, 1967, the National Center for Health Statistics.
[2]Health and Nutrition Examination Survey 1971 (preliminary data). Computed from unpublished preliminary data furnished by the National Center for Health Statistics.
[3]Survey of Fourteen Communities February, 1973-June, 1974. Hypertension Detection and Follow-up Study, the National Heart and Lung Institute.

Figure 4. **NATIONAL HEART, LUNG, AND BLOOD INSTITUTE HYPERTENSION AWARENESS AND CONTROL**

Further encouraging signs are a 50 percent increase in patient visits for high blood pressure between 1971 to 1975 and a 40 percent increase in first high blood pressure visits (new patients entering care). In the same period, patient visits for all causes rose only about 14 percent (Figure 5).

As shown previously in Figure 1, death rates for cardiovascular disease (CVD) and stroke have been declining since 1950. It is particularly interesting to note that one-third of the total decline in the CVD death rate has occurred since 1972. Attribution for this drop is difficult, but it seems reasonable to believe that the recent attention to hypertension control has contributed significantly.

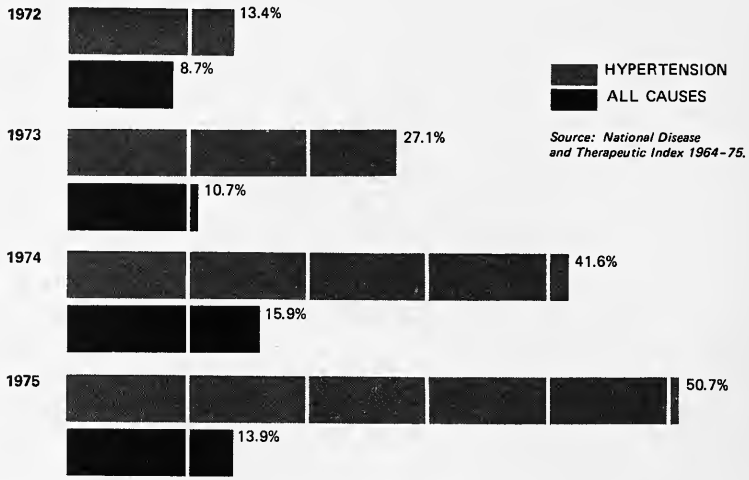


Figure 5. **PATIENT VISITS FOR ALL CAUSES AND FOR HYPERTENSION AND HYPERTENSIVE HEART DISEASE**
(Percent Increase Over 1971)

Prevention

The Prevention, Education, and Control Program is responsive to the National Heart, Blood Vessel, Lung, and Blood Act of 1972 which includes the mandate to promote the education and training of scientists, clinicians, and educators; the development and demonstration of diagnostic, treatment, and prevention approaches; and public education.

Considerable knowledge has been acquired in recent years concerning many of the diseases under the NHLBI mandate. To insure that these efforts do not go unexploited, the Institute has undertaken an active program of prevention, education, and control to speed this knowledge into the mainstream of clinical medicine. The NHLBI has acted in this new area of responsibility to develop the innovative approaches needed to carry out its mission. Advice and guidance are being sought from behavioral and social scientists, nutritionists, and others possessing skills not previously present within the NHLBI.

The NHLBI intent is to convey to the public and health care practitioners the latest knowledge, attitudes, skills, and technologies emerging from current practice and research so these may be promptly utilized in the maintenance of health, prevention, and treatment of cardiovascular, pulmonary and blood diseases.

To achieve its goals, this program has identified two objectives:

- To sponsor research and to develop and administer continuing education programs for health care professionals in the prevention and treatment of cardiovascular, pulmonary, and blood diseases
- To sponsor research and to develop and administer health education programs for the public and patients in the prevention and treatment of cardiovascular, pulmonary, and blood diseases.

PROGRAM STRATEGY AND TRENDS

Over the years, the programs of the Institute have evolved and materialized through a broadening of the investigator-initiated project base and through projects initiated by the NHLBI. From this evolution, trends have developed which will be pursued and augmented in the future.

The program strategy employed by the Institute for any individual disease includes an ordered sequence of:

- Acquisition of new knowledge (basic and clinical research)
- Testing and evaluation of promising hypotheses (clinical trials)
- Application of existing knowledge (education, demonstration, and control).

Progress has been made and continues to be made in each area of this overall strategy. Creative research by both individual investigators and by teams of investigators is leading to new knowledge about heart, blood vessel, lung, and blood diseases. Targeted research is being supported to attack problems urgently requiring solution in those situations where the underlying data base exists to make such research feasible. In addition, imaginative new approaches

are being developed and initiated to decrease the time needed for translation of this new knowledge into improved health care.

It cannot be overemphasized that the development of new knowledge through investigative research remains not only an area of continuing need, but also one of the highest priority. Such knowledge is the prerequisite for prevention and rational treatment of disease. No central authority can establish predetermined guidelines to obtain such knowledge. In the main, it can only be developed by individual investigators, working in small or large groups, following their own leads, and pursuing problems of their own choosing. History bears out the importance of such basic nondirected research in that our current level of knowledge and understanding has been provided in large part as a result of this kind of research.

II.
HIGHLIGHTS OF RECENT ACCOMPLISHMENTS

Progress has been achieved in many areas of heart, blood vessel, lung, and blood research since the initiation of the National Program in 1973, and important interrelationships among heart, blood vessel, lung, and blood diseases are emerging. Recent accomplishments of the National Program are summarized in this section. They represent the achievements of many scientists at the Institute and throughout the nation working cooperatively to improve our understanding of the causes of diseases and our methods for diagnosing, treating, and preventing diseases. The progress made will contribute substantially to improve health and prevent disease; in the process, deeper layers of unanswered problems requiring solutions have been uncovered.

ATHEROSCLEROSIS
... *One Possible Etiology*

The process leading to formation of the atherosclerotic lesion (plaque) is complex. Plaque development starts with an injury to the inner lining (endothelium) of an artery. The injury may be caused by mechanical denuding of the inner lining of the artery, for example, by the intraarterial shearing caused by high blood pressure.

A recent hypothesis that links many earlier unrelated observations proposes that the initiation and subsequent enlargement of atherosclerotic lesions require two interrelated cyclic events. The first cycle involves injury to the inner lining of an artery and its eventual healing. The second cycle occurs if the initial attempt at healing is followed by repeated injury. Such injury leads to repeated deposits of multiple layers of smooth muscle cells, intracellular and extracellular lipids (fats), and connective tissue, thereby increasing the size of the

lesion and causing it to protrude into the inner lumen of the artery. This protruding portion of the arterial wall is more susceptible to future injury, thus causing the injury cycle to repeat itself. During enlargement, calcium may also be deposited into the lesion resulting in a still more complex calcified atheroma. As the plaque enlarges it may block the inside of the artery, drastically impeding blood flow. This in turn may produce serious clinical sequelae--for example, heart attacks and strokes.

Experimental findings support the above hypothesis of a double cycle and indicate the direction of future research. Specifically, injury of the endothelium stimulates the growth of smooth muscle cells which form plaque, and experiments show that platelet factors are essential to smooth muscle cell proliferation after vessel injury. This role of platelets is being studied with the potential goal of developing platelet antiaggregating drugs which could prevent or reverse plaque formation.

ATHEROSCLEROSIS
... *Plaque Regression*

Atherosclerotic lesions similar to those in humans can be produced by a high-fat diet in nonhuman primates and other animals. Experiments have shown that plaque development can be reversed in these animals by diet manipulation and drugs which lower serum cholesterol levels. Plaques in Rhesus monkeys with severe atherosclerosis were reversed equally well by a low-fat diet and by a low-fat diet enriched with polyunsaturated fatty acids.

SMOKING HAZARD
... *Improved Animal Models for Risk Assessment*

Smoking has been identified as a major risk factor related to atherosclerotic heart and vascular diseases. Studies are in progress to develop less harmful cigarette products using tobacco substitutes. As part of this program, nonhuman primates have been taught to smoke and to inhale as humans do. A number of such trained animals are being used as models for studying the disease-producing effects of both available and newly developed cigarettes. In addition, the NHLBI is cooperating with the National Cancer Institute (NCI) in efforts to evaluate less hazardous cigarettes.

NUTRITION AND HEALTH
... *Better Information on Food Composition*

Institute nutritionists, working with nutritionists in other governmental and nongovernmental agencies, have made progress in the important task of updating and disseminating information on the composition of foods as they are relevant to heart and vascular disease. The NHLBI Table of Food Composition[1] has been developed with particular emphasis on the delineation of fats and cholesterol. Recognizing that current data on food composition are inadequate, the Institute is funding a review of literature and collection of data on food lipid

composition. Fatty acid data have been summarized for milk and other dairy products, eggs and egg products, beef, fin fish, and cereal grains. Working with nutritionists of the American Diabetes Association, the American Dietetic Association, and the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), the NHLBI staff have revised the publication "Meal Planning and Exchange Lists" for use in nutrition counseling. The revised publication updates the information on food composition and therefore provides an improved aid for patient counseling. The revision also promotes the use of the fat-control aspect of the diet for treatment of diabetes and other diseases for which quantitative and qualitative diets are advised.

BEHAVIOR RESEARCH
... *Techniques for Achieving Adherence to Treatment*

Some information is available about effective weight reduction and smoking cessation, but very little well-based information is available to guide physicians on how to persuade patients to take prescribed medication for high blood pressure control. The Institute's National High Blood Pressure Education Research Program (NHBPERP) is studying the factors that positively influence the patient to continue to take prescribed drugs.

A number of promising, but preliminary, findings have emerged. For example, an interesting way to achieve adherence behavior is for the physician, nurse, or other health provider to enter into a written "behavior contract" based on a "reward" and "cost" exchange for success and failure. This behavioral research has also found that sending health workers into the home is twice as effective in enhancing adherence behavior as small group education in the medical clinic. However, both of these treatments were significantly more effective in maintaining lowered blood pressures than treatment in a routine medical care setting.

CORONARY HEART DISEASE
... *Possible Protective Factor*

Recent cross-sectional and prospective studies indicate that although high levels of lipoproteins in the blood are associated with increased risk of coronary heart disease, one kind (high-density lipoprotein, or HDL) correlated inversely with the risk of developing coronary heart disease. Recent biochemical investigations suggest that HDL is involved in removing cholesterol from the arterial wall or in preventing its deposition.

CORONARY HEART DISEASE
... *Risk Prediction in the Elderly*

The Framingham Study provides unique data on the incidence of coronary heart disease (CHD) in men and women 49 to 82 years old. A continuous in-depth medical history of these patients covering 28 years is available. For this age group, a risk profile for CHD can now be developed by combining the following seven parameters: the blood levels of low-density lipoproteins, high-density lypoproteins, and triglycerides, systolic blood pressure,

enlargement of the left side of the heart, relative weight, and diabetes. Less than 2 percent of the CHD events were found in the 10 percent of the population thought to be at lowest risk, whereas 30 percent of the CHD events were found in the 10 percent of this population deemed at highest risk. These data show for the first time that CHD risk can be reliably determined in this older age group.

CARDIAC ACTIVITY
... *Direct Observation during Exercise*

The coordinated efforts of intramural scientists and physicians from the NHLBI, the Division of Computer Research and Technology, and the Nuclear Medicine Department of the National Institutes of Health Clinical Center have resulted in a new technique for viewing the heart by computer-based movies before, during, and immediately after exercise. A small amount of radioactive serum albumin is injected into a peripheral vein, an instrument to measure radioactivity is placed over the patient's chest, and the isotope emissions from the heart are localized by a computer. Motion pictures of the radioactive heart are produced while the patient is at rest or exercising, and simultaneously a time-activity curve which indicates precise changes in left ventricular volume with time is recorded. This new technique, called radionuclide cineangiography, for the first time enables actual visualization of the beating heart during exercise. The technique allows detection of abnormalities and diagnosis of coronary artery disease even in asymptomatic patients who have normal cardiac function at rest. Moreover, in persons with known coronary disease, it enables the assessment of the degree of functional impairment caused by specific coronary artery lesions and evaluation of the effects of therapy. The procedure offers less risk than cardiac catheterization and is a much more sensitive means for detecting cardiac disease in asymptomatic persons than older techniques involving an exercise electrocardiogram.

SUDDEN CARDIAC DEATH
... *A Better Prognosis*

Patients at high risk of sudden death after a myocardial infarction are being identified with increasing accuracy. The monitoring of electrocardiograms, especially late in the hospital course, has improved the identification of patients with serious ventricular arrhythmias that can precipitate sudden cardiac death. Preliminary trials show that antiarrhythmic drugs, especially those that block the beta-adrenergic system, may prevent fatal cardiac arrhythmia from developing. Wider implementation and more effective use of this therapeutic procedure in emergency care systems will save many lives that would otherwise be lost before a hospital can be reached.

HEART ATTACK
... *Rapid, Accurate Diagnosis*

When a heart attack occurs, tissue is damaged. Rapid diagnosis of heart attack and measurement of cardiac damage are essential to optimal treatment.

Identification of an isoenzyme of creatinine phosphokinase (CKP-MB) released into the blood stream after heart muscle damage, now enables the accurate diagnosis of cardiac damage in the absence of EKG changes. A recently completed clinical study attests to the superiority of this new method of diagnosis.

EMPHYSEMA
... Improved Understanding

Emphysema is a disease in which the thin walls of the air sacs (alveoli) lose their elasticity, and tear. One area of concentrated research has been to determine the structure of lung elastin, which is an essential fibrous protein of the lung responsible for contraction and expansion. Progress has been made in isolating and further understanding both lung elastin and its precursors in the biological process. Studies of elastin have been aided by the use of synthetic inhibitors which prevent its dissolution by the enzyme elastase. The Division of Lung Diseases has distributed such synthetic inhibitors to more than 30 lung pathologists for additional studies of lung elastin.

NEONATAL RESPIRATORY DISTRESS SYNDROME
... Prenatal Diagnosis

Neonatal Respiratory Distress Syndrome (NRDS), commonly known as hyaline membrane disease, is a disorder of the newborn which is characterized by immaturity of the lung. It is usually associated with prematurity, and the symptoms start within hours of birth. Unless specialized treatment is provided, the disease frequently leads to death within a few days. Since this is a disease of prematurity, it is especially important that it be diagnosed before birth so that preparation can be made for suitable treatment of newborns who are at risk.

The presence of surface active protein material (SAM) is necessary for the terminal airways of the lungs to maintain their function and structure. This protein is present in amniotic fluid and its concentration in the fluid reflects the functional capacity (maturity) of the fetal lung. A new rapid, reliable, and inexpensive method of quantifying SAM in human amniotic fluid holds great promise of providing a superior means for early detection of NRDS.

CYSTIC FIBROSIS
... Improved Understanding

Cystic fibrosis is a genetically determined disease that affects many organs, and the resultant chronic lung disease is a major source of morbidity and mortality. Cystic fibrosis is characterized by an excessive production of mucus, and it was formerly fatal in early childhood. However, with advances in therapeutic techniques, those afflicted sometimes now live into adolescence and even beyond, although severely handicapped by this disorder.

Because of the significance of excessive mucus in this disease, it is important to study the properties and production of the mucus. A technique has

been developed which may make it possible to study mucus at the location where it is produced. This technique for direct visualization of changes at the site of mucus production is an important advance over the previously available methods which depended on the analysis of sputum in which the mucus may be significantly modified. Moreover, the study of factors involved in secretion of mucus is also important for an understanding of other lung diseases which are also associated with excessive mucus production, especially chronic bronchitis and asthma.

CHRONIC OBSTRUCTIVE LUNG DISEASE
... *Effects of Smoking Cessation*

Recent studies provide additional encouraging evidence that the cessation of cigarette smoking will not only arrest, but also may actually reverse, some of the adverse effects of cigarette smoking on lung function. Pulmonary function was assessed before and after cessation of cigarette smoking in a 16-month study of more than 130 men and women who attended a smoking cessation clinic. Functional abnormalities in the participants were related to the lifetime history of smoking (pack years) rather than to peak cigarette consumption. When cigarette smoking was stopped or reduced there was a significant improvement in pulmonary function measured by tests that determine abnormalities in both the large and small airways. Although the study has not yet progressed long enough to determine whether or not lung function will return to normal levels after smoking ceases, it is encouraging that distinct benefits can be derived for those who already have abnormalities of lung function by the elimination or reduction of cigarette smoking.

PULMONARY FIBROSIS
... *Role of Cigarette Smoking*

Pulmonary fibrosis is the result of the proliferation of connective tissue or scar formation in the lung. One of the main defense mechanisms against types of injury which lead to pulmonary fibrosis is a cell known as the alveolar macrophage: this cell engulfs invading foreign particles. Recent studies have found particles in alveolar macrophages which are similar to particles found in other lung cells (interstitial cells) of smokers. Through examination by electron microscopy and X-ray spectrometry, fiberlike inclusions identified in the alveolar macrophages have now been shown to have a three-dimensional structure with the characteristics of kaolinite (an aluminum silicate). Since kaolinite is present in cigarette smoke, these findings provide a link between inhalation of such particles in cigarette smoke, their uptake by the alveolar macrophages, and their transport to and deposition in the lung interstitial cells. This suggests a possible relationship between cigarette smoking and pulmonary fibrosis in the interstitial cells of smoker's lungs.

CHRONIC OBSTRUCTIVE LUNG DISEASE
... *Improved Detection of Early Abnormalities*

Because chronic obstructive lung disease (COLD) such as emphysema or chronic bronchitis, is usually irreversible if it is not detected before the appearance

of clinical symptoms, it is important to detect functional abnormalities early in the course of the disorder. Two methods of accomplishing this have been developed. One of these is an inexpensive breathe-through carbon monoxide meter, which is capable of measuring uptake of carbon monoxide during a single breath at rest and during exercise. The device is sensitive enough to evaluate regional defects in the pulmonary capillary bed. This simple screening test for lung function can now be used to diagnose pulmonary emphysema before the appearance of symptoms. The other method is a radiographic technique, microfocal spot magnification, which provides the possibility of direct visualization of the early alterations associated with airways obstruction. This technique can be used to visualize the smallest lung units in animal and postmortem human lungs, and it holds promise for extension to use with patients for early detection of changes that lead to chronic obstructive lung diseases.

CENTRILOBULAR EMPHYSEMA
... *Etiology in Cadmium Workers*

A deficiency of the proteinase inhibitor, alpha-1-antitrypsin, has been identified as a factor in the development of a severe form of familial emphysema which attacks young adults. A recent study indicates that the trace metal cadmium can inactivate alpha-1-antitrypsin when mixed with serum at concentrations comparable to those found in the blood stream of cadmium workers. This is a significant finding in light of the fact that industrial exposure to cadmium is often associated with the development of severe centrilobular emphysema. The study suggests that the underlying cause of this industrially induced emphysema is the inactivation of alpha-1-antitrypsin. This knowledge may allow for the development of protective or therapeutic measures.

PULMONARY VASCULAR DISEASE
... *Therapy*

Digoxin is a drug used to increase the force of heart muscle contraction in cardiac patients. However, in patients with concurrent lung disease, this drug has significant adverse effects. The reason for this may be explained by the observation that during hypoxia (oxygen deficiency), digoxin increases the sensitivity and contractibility of pulmonary vascular smooth muscle and thus contributes to the elevation of pulmonary artery pressure. Although higher pulmonary artery pressure may improve perfusion in the lung, it also increases the burden on the right side of the heart, thereby causing the observed toxic effects.

CHRONIC OBSTRUCTIVE LUNG DISEASE
... *Epidemiological Studies*

Three population groups totaling 7,203 individuals--a rural area without industry, a large urban area with a high pollution level, and a small residential town with minimal industrial activities--are under study to assess the prevalence of chronic obstructive lung disease as a function of age, sex, socioeconomic status, and environment. Preliminary analyses of the data indicate

that respiratory symptoms and lung function measures are more closely associated with smoking habits than with area of residence. It has also been documented that socioeconomic status is a significant factor in both symptom prevalence and in respiratory function.

BLOOD OXYGEN LEVEL
. . . Monitoring in Sick Infants

Preliminary results from the continuous monitoring of sick newborns using an oxygen pressure sensor device have shown unexpected and clinically significant variations in arterial oxygen tension. These results show that the blood oxygen levels of an infant at rest with a stable heart rate and respiratory pattern can vary significantly. Crying and simple manipulations of the infant such as taking of vital signs, physical examinations, and endotracheal suctioning to clear the lungs of mucus all result in decreases of the blood oxygen level which may take up to seven minutes to normalize. These findings demonstrate that isolated blood gas samples do not give blood oxygen level values that are representative of the infant's oxygenation. They also suggest that changes in the management of sick newborn infants could have important effects on their recovery rate.

PULMONARY EDEMA
. . . Improved Detection

Pulmonary edema, a condition in which there is abnormal extravascular storage of fluid in the lungs, can now be rapidly and accurately detected by measuring alterations in lung weight. A mass spectrometer coupled with a minicomputer permits noninvasive measurements on patients in ventilators as well as on those breathing spontaneously. Because of its accuracy, portability, and speed it is a valuable device for detecting early signs of pulmonary edema and for following the effects of therapy.

PULMONARY VASCULAR PRESSURE
. . . Noninvasive Measurement

In order to detect and treat pulmonary vascular disease it is important to be able to measure the pulmonary artery pressure. Three new approaches of measuring pulmonary artery pressure are under development. In the first method, echocardiography is being used to measure the motion of the cardiac valve between the pulmonary artery and the heart. A mathematical analysis of the characteristics of this valve motion enables the calculation of the estimated pulmonary artery pressure. A second method, the bubble ultrasonic resonance pressure (BURP) technique, utilizes the knowledge that the radii of gas bubbles in fluid vary with pressure. The changes in the radii of the bubbles can be measured by sonar devices. The third method involves Doppler flow techniques to determine blood flow and blood pressure.

PULMONARY EMBOLISM
... A New Treatment

Pulmonary embolism is the obstruction of a blood vessel in the lung by a blood clot that formed previously elsewhere in the circulation, e.g., in the leg. An embolism can now often be removed from patients by the use of a vacuum catheter. The catheter is introduced into the lung via right heart catheterization. This technique makes it clinically feasible to remove pulmonary emboli in critically ill patients without open heart surgery.

RESPIRATORY FAILURE
... Improved Detection

Respiratory failure is a potentially fatal consequence of a variety of acute and chronic respiratory disorders, but it is reversible if diagnosed early and treated promptly. Moment-to-moment monitoring of blood gases is the most effective way of detecting changes associated with the onset of respiratory failure and for determining the efficacy of therapeutic interventions. Sensor technology has now been developed to the point that blood gases can be measured continuously by techniques that are both rapid and accurate. After extensive animal studies of these techniques, clinical trials with patients have been initiated. It is anticipated that it may soon be possible to continuously measure blood gas changes in patients early enough to detect the onset of acute respiratory distress syndrome and to assess progress once therapy is introduced.

LUNG DISEASE
... Dissemination of Knowledge

Self-instructional programs addressed at recognition and early treatment of respiratory insufficiency have been developed for physicians and others involved in emergency medical care and respiratory intensive care. One highly portable program package is designed to train policemen, firemen, and other first responders, as well as hospital-based health care personnel. The package includes materials sufficient to lead the student through the course without an instructor. Another self-instructional program uses computer simulation of a patient in various stages of respiratory failure. The student treats the patient, and the immediate consequences of his therapeutic measures on the status of the patient are played back on the computer. Thus, instructional feedback of the value of various procedures is provided to the physician or nurse without incurring risk to a real patient.

LUNG DISEASE
... Demonstration Project

A "clinical monitoring bed" is being developed at the Vermont National Research and Demonstration Center for Lung Diseases. The monitoring system of the bed involves computer storage of sequentially acquired data on the patient

and an assessment of the trend of his disease. This will make available to community hospitals a more accurate means of assessing the progress or regress of respiratory disease patients who are at risk of respiratory failure. The goals are to anticipate complications and to determine therapeutic measures earlier in the course of the particular disease so as to avoid irreversible respiratory failure.

HEMOPHILIA AND VON WILLEBRAND'S DISEASE
. . . Factor VIII

Significant advances have been made in basic knowledge of the biochemistry of the factor VIII molecule which has now been partially purified and characterized. There are new procedures for isolating this substance from the blood in a highly concentrated form. Progress in elucidating the structure and mechanism of action of factor VIII should now be facilitated. This progress, in turn, should lead to better methods in the treatment of hemophilia and von Willebrand's disease.

BLOOD CLOTTING
. . . A Better Understanding

Sophisticated biochemical research has produced much data on the complex structure, function, and mode of action of circulating inhibitors of the activated clotting factors for blood-clot formation. How these inhibitors turn off the clotting system once it has fulfilled its task is now better understood at the molecular level. In addition, the molecular interaction of the anticoagulant heparin with one of these inhibitors has been elucidated, thus providing a rational basis for the use of heparin in the prevention and treatment of thromboembolic disease.

Until recently, vitamin K deficiency was thought to decrease the production of coagulation proteins and thereby lead to excessive bleeding or prevention of clotting. Many anticoagulant drugs (such as the coumarin derivatives) are Vitamin K inhibitors. The precise molecular mechanism of Vitamin K action has recently been elucidated. In addition to being a demonstration of a significant biological process, this discovery may pave the way for development of improved anticoagulant drugs.

ASPIRIN
. . . Mode of Anticoagulant Action

The clumping together of blood platelets occurs early in the series of events leading to the formation of a blood clot. Aspirin inhibits this platelet clumping and can thereby cause excessive bleeding in some patients or can act as an antithrombotic drug in others. The mechanism by which aspirin inhibits platelets has now been described at the cellular level: the drug inhibits an enzyme that catalyzes the formation of the platelet clumping agents, the thromboxanes.

VENOUS THROMBOSIS
... A Better Diagnosis

Small blood clots in veins are difficult to diagnose. A sensitive radioimmunoassay for fibrinopeptide A, a constituent of blood clots, has now been developed. This assay is a far more specific and sensitive indicator of clotting than other available methods and has proved most useful for the diagnosis of peripheral venous thrombosis.

DEEP VEIN THROMBOSIS
... Prophylactic Treatment

Deep vein thrombosis and pulmonary embolism are frequently complications of various conditions: medical disorders, surgical procedures, and trauma. These complications are responsible for widespread morbidity and considerable mortality. A workshop held in conjunction with the American Heart Association critically evaluated the large volume of data available on preventative therapy for venous thromboembolism. The resultant publication, Prophylactic Therapy of Deep Vein Thrombosis and Pulmonary Embolism,[2] has been widely disseminated. Recent research indicates that prevention of venous thromboembolism may be achieved through carefully controlled low-dose heparin therapy. The anticoagulant is given before surgery is begun and during the recovery phase until the patient is ambulatory.

SICKLE CELL ANEMIA
... Screening and Education

The Sickle Cell Screening and Education Clinics are increasing the awareness and understanding of sickle cell anemia and sickle cell trait. The clinics are developing and field-testing methods of information dissemination, screening, counseling, and patient referral in a variety of environments. Education and counseling protocols have been developed to assure content accuracy in educational presentations and counseling sessions.

Tutorial programs for students with sickle cell anemia initiated by the Comprehensive Sickle Cell Centers have resulted in decreased school absenteeism, in increased scholastic achievement, in decreased psychological pressures of adaptation, and in overall increased self-esteem. Vocational rehabilitation of patients with sickle cell anemia is provided through individual career counseling.

SICKLE CELL ANEMIA
... Improved Emergency Care

Emergency room care for sickle cell patients was evaluated at a large city hospital by one of the centers and was determined to be suboptimal. Related problems were often not recognized, and in other cases, there were misdiagnoses. A protocol has now been developed for emergency room care that deals with treatment, highlights symptoms, and considers various diagnoses. The resulting

increased awareness of the house staff, nurses, and aides, for example, has contributed to a marked improvement in the management of patients with sickle cell anemia in the emergency room environment. This protocol has been made available to other medical centers throughout the country.

SICKLE CELL ANEMIA
... Diagnosis and Treatment

To reduce morbidity and mortality from sickle cell anemia, there is a need for accurate diagnoses early in childhood, preferably in the newborn. This capability has been developed through the use of microcolumn chromatography which can identify sickle cell and other abnormal hemoglobins. Screening of cord bloods has been done in over 30,000 newborns, and many infants have been found to have sickle cell anemia. Close monitoring of these infants will alert physicians to the early symptoms of often fatal infections. The early identification of eye lesions and their treatment may significantly reduce blindness and other visual complications in sickle cell patients. New photographic contrast techniques have been developed for better detection of such lesions. Various modifications of treatment, including argon and xenophoto coagulation, are currently being investigated.

BLOOD RESOURCES
... Blood Safety Sterile Connecting Device

The need for red blood cells accounts for 70 percent of all blood transfusions. Red cells can be maintained for many months without loss in quality when they are stored in a frozen state; however, present methods for processing frozen-thawed blood and blood components including red cells do not guarantee sterility. Thus, a Food and Drug Administration ruling places a 24-hour outdating limit on blood once it has been thawed. Recognizing the need to maintain a disease-free atmosphere while processing blood and blood components, the Institute has developed and is testing an effective but inexpensive "sterile connecting device" that will permit storage of frozen thawed blood and blood components for a substantially longer time.

BLOOD RESOURCES
... Blood Substitutes

Blood substitutes have tremendous potential value in health care. Once developed for use, these preparations could eliminate the problem of transmittal of infectious agents through transfusions and could supplement and conserve the natural blood supply. The use of blood substitutes in emergency situations where blood may be in short supply or unavailable could be lifesaving. The results of animal transfusion studies with blood substitutes have been very encouraging. Primates can be maintained for several hours with up to 80 percent of their blood replaced with a synthetic-type substitute--for example, certain perfluoro-chemicals. Other animals have been maintained for longer periods with 90 percent of their blood exchanged with a natural-type substitute, cell-free hemoglobin. Animals completely transfused with a cell-free hemoglobin recover and continue to live a normal life after regenerating their own blood.

III.
RESOURCE ALLOCATION

As a result of the Act of 1972 and its renewal in 1976, the National Heart, Lung, and Blood Institute (NHLBI) has initiated or planned for new activities in a number of research areas. These expanding activities stem from an already viable program of the earlier National Heart Institute to which has been added responsibilities for lung diseases, blood diseases, and blood resources. In 1972, the Institute was elevated to bureau status and was also given the mandate to plan, lead, and coordinate the National Program involving heart, blood vessel, lung, and blood diseases, and blood resources.

Many of the Institute's ongoing programs, such as the centers programs and major clinical trials, have resulted in the exploration and definition of expanded opportunities in heart, lung, and blood research. Major opportunities and needs have developed in the demonstration areas. New interdisciplinary and collaborative initiatives such as the joint US-USSR programs and the first efforts in the area of behavioral studies are leading toward accomplishments that may have a profound impact on disease prevention. Increased reporting requirements, in addition to the expanding program activities, have amplified current and future monitoring and evaluation functions. Recent program evaluation activities have identified additional opportunities and needs. The Institute's program plan and ongoing activities thus are not held up by want of ideas or opportunities; rather, the availability of resources appears as the rate-limiting factor in implementation.

PROGRAM ACTIVITY AND FISCAL SUMMARY

Recent studies have provided a clearer insight into both the manpower and the facilities required for the successful development and scheduled implementation of the National Program. Recent, current, and projected allocations of resources are summarized and discussed below in connection with the major program components.

National Research and Demonstration Centers

National Research and Demonstration Centers (NRDCs) play an important role in achieving many of the goals of the National Program by bridging the gulf between fundamental research and the application of research results in health care and disease prevention. The presence in a single center of scientists, physicians, and other professional personnel representing many disciplines creates an environment in which participants can interact and train young scientists in an efficient and productive way.

In FY 74, after a nationwide competition, the National Heart, Lung, and Blood Institute awarded NRDC grants to three institutions:

- The Center at the University of Vermont, College of Medicine, melds and intensifies efforts and resources for the control of respiratory disease. This center features a program to produce statewide assistance in the management of pulmonary disease through a regional management structure employing an interhospital network for information storage, data interpretation and analysis, aids in diagnosis and treatment, and dissemination of new knowlege.

- The Baylor College of Medicine in Houston has a Research and Demonstration Center which focuses on heart and blood vessel diseases, particularly atherosclerosis. An important project deals with the application of the preventive treatments and rehabilitative procedures in the Baylor Cardiovascular Center to community clinics and hospitals.

- The National Research and Demonstration Center at the Puget Sound Blood Center in Seattle is concerned with the improvement of procedures for the acquisition, processing, storage, distribution, and clinical use of blood and blood products.

The programs of the three established centers encompass a spectrum of health-related activities and approaches. These are serving as a blueprint for the design of a second generation of centers. The NHLBI believes the time has now come to extend the scope and number of National Research and Demonstration Centers. The intent of the Congress has been made clear by reauthorizing appropriations in FY 76 to promote this program.

In FY 76, the National Heart, Lung, and Blood Advisory Council appointed a working group to develop guidelines for new National Research and Demonstration

Centers. This working group recommended a revised center concept that would provide for the coordination and integration of ongoing research and training efforts within the center. Moreover, this center concept would help to implement, expand, and coordinate national activities aimed at closing any existing translation gaps, and would bring the new findings from the research laboratory directly to the patient and his primary care physician.

A major criterion for NRDC designation is evidence of a genuine commitment to develop capabilities for validation and translation of innovations to the general public, high-risk populations, and providers of health care. A program announcement for this new Research and Development Center will be forthcoming in FY 77. The review and awards will be made in FY 78, and renewed competition will be scheduled for FY 81. The projection for the next five years* will reflect the magnitude of financial resources required to fund these centers.

Prevention, Education, and Control

The Office of Prevention, Education, and Control (OPEC) was created as an organizational entity within the NHLBI in response to the mandates requiring greater concern for the translation and dissemination of research results. The early objective of this office has been the identification of fruitful areas for NHLBI activity as well as the definition of resources for carrying out these activities. The OPEC has also served to assist the community in the development and implementation of prevention and health education programs. The behavioral patterns of both health professionals and the general public have been identified as probable key factors in successful prevention programs. Proceedings of four NHLBI-supported conferences and their recommendations have served as the impetus for the initiation of research in the health behavior area:

- Applying Behavioral Science to Cardiovascular Risk.[3] The purpose of this symposium was to examine the "state of the art" of behavioral science contributions to health behavior in general and to the reduction of risk of heart attack and stroke in particular. The proceedings gave evidence of an increasing ability on the part of the behavioral scientist to provide intervention strategies for large-scale efforts to influence health behavior.

- Proceedings of the Nutrition-Behavioral Research Conference.[4] The goals of the conference were to review the objectives, progress and results of each of the NHLBI nutrition, education, and intervention programs as well as to assess other research in this area. The conference discussed general principles and specific methods for producing dietary behavior changes that have emerged from recent research and recommended general aspects for use in segments of the population.

*See *Fiscal Summary*, pp. 38-39.

- Proceedings of the National Conference on Emotional Stress and Heart Disease.[5] This conference focused on the relationship of stress and strain as they relate to the human cardiovascular system. Attempts were made to define and correlate emotional stress with the pathophysiology of sudden death and myocardial infarction.

- Proceedings of the National Heart and Lung Institute Working Conference on Health Behavior.[6] The overall goals of this conference were to provide substantive information and advice to the Institute from the behavioral and social science community on health behavior problems related to the prevention and control of heart, lung, and blood disorders; and to provide opportunity for behavioral and social scientists to become intimately familiar with health behavioral problems extant in the heart, lung, and blood areas.

In addition to conferences, the Institute has initiated a Task Force on Prevention, Education, and Control for Pulmonary Diseases. The task force report to be released this year will outline the issues of primary concern in the area of chronic lung diseases. A task force in the area of prevention, education, and control of heart and vascular diseases is also underway and will make its recommendations in FY 77. A blood task force will begin its deliberations within the next fiscal year. The recommendations of these conferences and task forces will be used to develop research education and demonstration programs in FY 78 and beyond.

Clinical Trials

The attack on heart, blood vessel, lung, and blood diseases extends across many fundamental and applied disciplines and includes a wide spectrum of activities including "basic" research, clinical investigations, epidemiology, preventive trials, and clinical medicine. The need to make advances in these areas available to the population at large has become widely recognized in recent years. The NHLBI uses many methods to test and evaluate basic research findings and hypotheses. The large-scale multicenter clinical trial is an indispensable method which the NHLBI has used to assess the efficacy and applicability of research results. Clinical trials, through their careful accumulation and critical analysis of data, lead to more rational and effective medical practice with less reliance on simple empiricism.

Clinical trials are an effective means and, in fact, often the only means of resolving particularly pressing scientific problems. While resource commitments are large, costs in manpower and money are justified if a definitive answer to a significant question (or questions) can be obtained more expeditiously or accurately through these studies than through other means of research investigation.

However, one should not lose sight of the fact that clinical trials commit the Institute to outlays in terms of budgets and staff for monitoring and review that far exceed those needed for the administration of other projects, such as regular research grants and research contracts.

Thus, clinical trials require a long-term commitment which "ties up" manpower, facilities, and resources for the participating extramural research community. Also, the conduct of a clinical trial requires interaction with the community participating in the trial and with the research staff assuring motivation of trial participants and their adherence to trial regimens so that after a prescribed number of years final answers will be obtainable.

The typical NHLBI Clinical Trial involves a cooperative effort in which investigators in a number of institutions follow a common protocol and work within a clearly defined structure. Major clinical trials supported by the Institute are listed below. Essentially all began after the initial passage of the Heart, Lung, and Blood Act in 1972. In FY 76, over $46 million, or one-eighth of the Institute's total budget, was spent on multicenter clinical trials which included:

- Aspirin Myocardial Infarction Study (AMIS). Study involving 30 clinical centers to determine whether administration of aspirin to persons who have had at least one documented heart attack will result in a significant reduction in cardiovascular morbidity and mortality

- Coronary Artery Surgery Trial (CAST). Trial involving 16 clinical centers to evaluate the efficacy of coronary artery bypass surgery and its potential therapeutic effect in reducing morbidity and mortality in coronary artery disease

- Hypertension Detection and Follow-up Program (HDFP). Program involving 14 clinical centers to determine in the general population the extent to which mortality and morbidity associated with elevated blood pressure can be reduced by systematic antihypertensive drug management

- Coronary Primary Prevention Trial (CPPT). Trial involving 15 clinical centers to determine if reduction of cholesterol by drug therapy will significantly lower the incidence of atherosclerotic coronary heart disease in a group of hypercholesterolemic, but otherwise healthy, men

- Multiple Risk Factor Intervention Trial (MRFIT). Investigation involving 20 clinical centers to determine whether a preventive program directed at the reduction of serum cholesterol, reduction of blood pressure, and reduction or elimination of cigarette smoking among a specific group of "high-risk" men will significantly reduce the incidence of myocardial infarction and death from coronary disease

- Prevention of Neonatal Respiratory Distress Syndrome (NRDS) with Antenatal Steroid Administration. Trial involving over 5 centers to determine if the incidence, morbidity, and mortality from neonatal respiratory distress syndrome can be reduced in infants at risk by antenatal administration of steroids and whether any sequelae in survivors can be attributed to steroid therapy

- Cooperative Study of Spontaneously Occurring Factor VIII Inhibitors in Patients with Hemophilia. Study to obtain data on the occurrence and natural course of the factor VIII inhibitor, to correlate inhibitor behavior with the clinical course, and to study complex inhibitors

- Extracorporeal Membrane Oxygenator Study (EMOS). Multicenter study to examine and evaluate the indications for the use and efficacy of extracorporeal membrane oxygenators for the support of patients with potentially reversible acute respiratory failure

- The NHLBI Veterans Administration Clinical Trial in Mild Hypertension. Collaborative study involving several VA hospitals testing the feasibility of conducting a large-scale trial to determine whether treatment of mildly elevated blood pressure reduces the incidence of heart attack in the study populations

- Nocturnal Oxygen Therapy Trial. A six-center study to evaluate the efficacy of nocturnal low flow oxygen therapy, in contrast to continuous therapy in patients with chronic hypoxic lung disease and cor pulmonale.

Because of their importance and relevance to the health care of all Americans, the Institute will be initiating additional clinical trials in the next fiscal year. These new trials include:

- A study to examine the effects of an antiarrhythmic drug (propranolol) on sudden cardiac death and total mortality in patients recovering from acute myocardial infarction

- A study to evaluate techniques to protect ischemic myocardium and minimize the amount of permanent heart muscle damage associated with acute myocardial infarction

- A study to evaluate the effects of long-term, intermittent positive pressure breathing (IPPB) treatment when used as an adjunct to the overall care of ambulatory patients with chronic obstruction pulmonary disease (COPD).

Activities Related to the National Program

In addition to the activity areas outlined above, further funding and supporting staff have been and are still required for new activities including:

- The Management and Support of Specialized Centers of Research (SCORs) in Heart, Lung, and Blood Diseases. These Specialized Centers of Research were instituted to advance basic knowledge and to generate the most effective techniques and methods of clinical management and prevention in the areas of arteriosclerosis, hypertension, ischemic heart disease, pulmonary diseases and thrombosis.

- Management of the Interagency Technical Committee (IATC) and other Interagency Activities Related to the National Program. Working groups to the IATC have been documenting federal agency coordination of pediatric pulmonary diseases, hypertension, sickle cell diseases and nutrition. Additional areas for interagency cooperation have been identified. Many projects addressing one or more program areas of the National Program have been pursued through formalized interagency agreements.

- Management of International Activities Related to the National Program. Currently, the Institute participates in active bilateral agreements with the USSR and the Federal Republic of Germany while informal exchanges exist with multiple foreign nations. The NHLBI coordinates its activity with those of the World Health Organization and many international scientific organizations.

- The National High Blood Pressure Education Program (NHBPEP). This Program is coordinated by the NHLBI. The coordinating mandate, as opposed to a direct operations mandate, is critical to both the activity and the success of the NHBPEP. All recommendations promulgated by the Program are developed through participation of relevant agencies and professional societies. This participation often results in uniform adoption of policies and achieves greater and longer-lasting coordination than any attempts at program direction by the NHLBI.

  Although most such efforts involve task-oriented short-term groups, an ongoing function is served by the High Blood Pressure Coordinating Committee. Comprised of major professional, voluntary, and consumer groups with a direct interest in hypertension control, the committee serves as a mutual

forum for all participants to identify priority issues and to develop together policies addressing the issues. The decisions of the group influence the efforts of all participants to the extent that the resources and missions of each permit.

- Coordination of the National Sickle Cell Disease Program. This program is a major collaborative effort by the National Institutes of Health (NIH), the Health Services Administration, the Center for Disease Control, the Department of Defense, and the Veterans' Administration to accelerate research in, and to improve diagnosis, education, control, and treatment of, sickle cell anemia.

- Activities Related to the Annual Updating of the Five-Year National Program Plan as Required by the Act. These activities include review of the status, progress, and updated plan of the National Heart, Blood Vessel, Lung, and Blood Program by the staff of the NHLBI with special inputs provided by the NHLBI Advisory Council and Technical Advisory Committees. The effort also includes preparation of an annual Report of the Director of the NHLBI.

- Manpower Training. Resources Available to the National Heart, Lung, and Blood Institute provide support to young scientists and physicians for research training in fundamental and clinical sciences associated with the disease areas which are the responsibility of the Institute. These manpower training programs increase the number and the competency of investigators in the biomedical disciplines essential to the advancement of knowledge in the cardiovascular, lung, and blood areas. A current summary of NHLBI manpower programs is provided in Table 5. The Institute, by its own initiatives as well as through cooperation with the National Academy of Sciences, continues to assess the manpower needs of the National Program and to determine areas in which a critical manpower pool is lacking. Most recent analyses indicate that the scientific manpower needed to support the full range of programs defined by the National Program is deficient in a number of areas. In 1972 and 1973, there were reductions in the overall number of training awards in support of NHLBI programs. While this trend has now been reversed (see Table 6) and the existing pool is expected to provide adequately for some program area needs, critical research areas such as epidemiology, behavior, nutrition, blood banking, academic cardiology, and pulmonary diseases are thwarted by shortages of specialized personnel. Training programs are planned during the next five years to alleviate these shortages.

Table 5. NHLBI FY 76 MANPOWER PROGRAMS, NUMBERS, AND OBLIGATIONS (Dollars in Thousands)

Activities	DHVD[1]		DLD[2]		DBDR[3]		Total	
	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount
Postdoctoral and Special Fellowships	–	$ 5	–	$ 3	1	$ 15	1	$ 23
Individual Research Training Fellowships (Weinberger)	23	238	8	151	12	177	43	566
Individual Research Service Awards (NRSA)	118	1,628	49	619	26	327	193	2,574
Institutional Research Service Awards (NRSA)	45	4,375	33	2,488	28	1,930	106	8,793
Graduate Training Grants	55	5,429	22	1,974	8	695	85	8,098
Pulmonary Faculty Awards	–	–	6	398	–	–	6	398
Subtotal	241	$11,675	118	$5,633	75	$3,144	434	$20,452

[1] The Division of Heart and Vascular Diseases.
[2] The Division of Lung Diseases.
[3] The Division of Blood Diseases and Resources.

Table 6. NHLBI MANPOWER PROGRAMS, FY 70-76 (Number of Trainees, Full-time Equivalent)

PROGRAMS	1970	1971	1972	1973	1974	1975	1976
Fellowship Programs							
Postdoctoral and Special Fellowships	176	168	144	72	36	10	1
Individual Research Training Fellowships (Weinberger)	–	–	–	–	167	56	43
Institutional National Research Service Awards (NRSA)	–	–	–	–	–	138	193
Subtotal	176	168	144	72	203	204	237
Graduate Training Programs							
Traditional Graduate Training Grants	980	1,012	980	880	852	552	340
Individual National Research Service Awards (NRSA)	–	–	–	–	–	279	491
Pulmonary Faculty Awards	–	–	–	–	–	24	24
Subtotal	980	1,012	980	880	852	855	855
Total	1,156	1,180	1,124	952	1,055	1,059	1,092

Investigator-Initiated Programs

To properly initiate the newly mandated programs discussed above within the resource allocations available, the National Heart, Lung, and Blood Institute has had to encroach upon some major areas of vital importance to the National Program. Among these program areas is the Investigator-Initiated Research Grant (IRG) Program. As shown in Table 7, the percentage of investigator-initiated grants awarded from among those approved because of their high scientific merit and program relevance decreased from 78 percent in FY 69 to 52 percent in FY 75. The FY 76 approval rate of 60 percent represents a slight reversal of this previous downward trend but is lower than the rate before the Act of 1972 indicating that the award rate since 1972 has not kept pace with the upsurge of worthwhile research proposals.

Table 7. NUMBERS OF INVESTIGATOR-INITIATED NHLBI RESEARCH GRANT APPLICATIONS, APPROVALS, AND AWARDS, FY 69-76
(R 01's ONLY*)

GRANT ACTIVITY	1969	1970	1971	1972	1973	1974	1975	1976
Applications	1,047	1,016	1,107	1,154	1,255	1,463	1,458	1,495
Approvals	615	616	714	753	887	1,084	1,084	1,081
Awards	481	436	431	467	405	573	568	648
% Approved Awards	78	71	60	62	46	53	52	60

*R 01's refer to traditional research projects usually initiated by individual investigators.

Fiscal Summary

As indicated in Table 8, the NHLBI research support in 1976 is two and one-third times the 1970 level. Nevertheless, the NHLBI percentage of the NIH total research support has remained constant at 16 to 17 percent since 1970. Yet during this period, the Institute has taken on the responsibility for the lung and blood research programs as well as for coordination of the National Program--responsibilities that entail substantially increased and costly program activities.

At any given time, the application of national resources must be determined in relationship to other important competing national priorities. In Tables 9 and 10 the resource allocation information reflects this fact and presents two alternative budgets which in the Institute's judgment best meet the

objectives of the National Plan. The budget of Table 9 builds upon the plan's past accomplishments, exploits new opportunities, and responds to such important congressional mandates as the further development of National Research and Demonstration Centers. The budget resource allocation plan presented in Table 10 is in the Institute's opinion a lower-bound budget for the NHLBI. The budget plan does not exclude, but postpones, the funding of valuable programs to future years. It defers the funding of National Research and Demonstration Centers, prevention, education, and control activities, manpower development programs, and construction. It also provides for a moderate decrease in extramural and intramural research programs. Research management and program services are adjusted accordingly.

Table 8. NIH RESEARCH SUPPORT, FY 70-77

ORGANIZATION	1970	1971	1972	1973	1974[1]	1975[1]	1976[2]	1977[3]
	Dollars in Millions[4]							
Total NIH Budget[5]	$1,030	$1,181	$1,466	$1,484	$1,947	$2,044	$2,186	$2,412
NHLBI	160	195	233	256	327	325	369	397
All Other B/I/D[6]	870	986	1,228	1,228	1,620	1,719	1,817	2,015
	Percentage Distribution of Funds							
Total NIH Budget	100	100	100	100	100	100	100	100
NHLBI[7]	16	17	16	17	17	16	17	16
DHVD[8]	(10.8)	(10.5)	(9.5)	(9.9)	(9.9)	(9.2)	(9.7)	(9.2)
DLD[8]	(0.8)	(1.4)	(1.6)	(1.8)	(2.3)	(2.2)	(2.3)	(2.2)
DBDR[8]	(1.3)	(1.7)	(2.2)	(2.7)	(2.6)	(2.4)	(2.6)[9]	(2.5)[9]
All Other B/I/D[7]	84	83	84	83	83	84	83	84

[1] Includes release of impounded FY 73 funds

[2] Excludes transition quarter

[3] Estimates.

[4] Not adjusted for inflation

[5] Excludes National Library of Medicine, Buildings and Facilities, and Office of the Director, NIH.

[6] Bureaus/Institutes/Divisions.

[7] Amounts are given as percentage of total NIH budget

[8] NHLBI budget includes Division of Heart and Vascular Division (DHVD), Division of Lung Diseases (DLD), Division of Blood Diseases and Resources (DBDR), as well as direct operations, program management, and intramural research.

[9] Includes Biomaterials Program ($3.5 million).

Table 9. **PROJECTED RESOURCE ALLOCATION* FOR THE NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM, FY 78-82**
(Dollars in Millions)

PROGRAM ELEMENTS	1978	1979	1980	1981	1982
Extramural Research Programs					
Heart and Vascular Diseases	233.0	241.8	243.8	249.0	251.0
Lung Diseases	53.0	57.5	59.0	63.0	65.0
Blood Diseases and Resources	60.0	64.0	66.0	70.0	72.2
National Research and Demonstration Center	40.5	47.9	50.3	71.5	73.0
Prevention, Education, and Control Programs	31.4	35.6	38.2	41.0	43.3
Manpower	35.0	37.0	39.3	43.3	45.0
Construction	32.0	35.0	35.0	0	0
Intramural Research Program	37.8	38.8	39.6	40.8	42.0
Research Management and Program Services	30.0	31.5	32.9	33.9	34.5
Total	552.7	589.1	604.1	612.5	626.0

*These tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.

Table 10. **PROJECTED LOWER BOUND RESOURCE ALLOCATION* FOR THE NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM, FY 78-82**
(Dollars in Millions)

PROGRAM ELEMENTS	1978	1979	1980	1981	1982
Extramural Research Programs					
Heart and Vascular Diseases	227.8	232.6	238.2	242.0	251.2
Lung Diseases	49.9	53.7	57.3	59.5	63.0
Blood Diseases and Resources	54.3	58.7	62.1	65.6	69.2
National Research and Demonstration Center	15.0	17.1	19.2	24.0	28.0
Prevention, Education, and Control Programs	22.0	24.3	27.7	32.7	36.8
Manpower	28.5	32.3	34.0	35.8	38.9
Construction	0	0	0	0	0
Intramural Research	35.6	36.6	37.0	38.8	39.9
Research Management and Program Services	28.5	29.0	29.5	30.9	31.9
Total	461.6	484.3	505.0	529.3	558.9

*These tabulations give the primary thrust of activities, even though these activities generally involve more than one subprogram.

NHLBI STAFF ALLOCATION PLAN

Since the enactment of the Institute's new legislative mandate in 1972, the NHLBI has suffered a personnel shortage. As early as 1973, at the time of submission of the First Annual Report of the Director of the National Heart and Lung Institute,[7] the personnel need for 1976 was estimated to be 810. In 1976, some relief was realized when our position ceiling was increased to 747. However, even this increased ceiling does not meet the needs under the current Institute mandates.

In response to the Act, the Institute has initiated activity in a number of new areas. Many new programs, especially the many clinical trials and targeted activities, require a high ratio of manpower to dollars. To operate the National Program effectively, the NHLBI needs additional staff both at the middle and upper professional levels as well as in support positions. Programs such as disease prevention, control, and education, and comprehensive centers are new to the Institute. Their review, administration, and evaluation require new staff with different knowledge and skills than those previously available within the Institute.

From FY 68 to FY 76, appropriations increased by 120 percent from $168 million in FY 68 to $370 million in FY 76. In the same period, the number of positions increased by only 23 percent, from 608 to 747. Despite this small staff increase, several congressional mandates for important programs were implemented.

To initiate these extensive new programs within the available manpower resources, the Institute has conserved manpower in several ways. The Division of Technological Applications was abolished and its activities divided among the three categorical scientific divisions. The review function for programs supported by the grant and contract mechanism were centralized, and a number of top-level personnel took on dual organizational functions. Staff was taken from established ongoing programs to meet new program needs. This latter technique, however, has now exhausted all ongoing program flexibility and has left the Institute staff perilously overdeployed.

IV. STATUS OF PROGRAM AND UPDATED FIVE-YEAR PLAN

HEART AND BLOOD VESSEL DISEASES

Coronary heart, cerebral vascular, and peripheral vascular diseases are major causes of disability and account for approximately half of all deaths in the United States each year. In recent years, particularly since 1970, the mortality from all diseases has decreased in the United States. However, as shown in Figure 1, the recent decrease in mortality from cardiovascular disease is substantially greater than the decrease from all other causes combined. This decreased mortality possibly results from better management of disease when it occurs coupled with the awareness and adoption of healthier life styles. Thus, both through possible delay of onset of disease and improved treatment when it occurs, the quality of life for those afflicted with chronic cardiovascular disease has improved in recent years. During this same period, the probability of an acute heart attack being fatal has also decreased. This downward trend in disease morbidity and mortality appears to be continuing.

Within the past three decades, major strides have been taken to identify individuals at high risk for atherosclerotic diseases. A number of risk factors for cardiovascular disease have been identified. These include elevated blood cholesterol, high blood pressure, cigarette smoking, and diabetes. Progress has also been made in the treatment of victims of heart disease. However, since many of the first manifestations of these diseases are acute with either death or irreversible damage to the brain or heart occurring suddenly, much attention has focused on the prevention and etiology of these diseases. The hoped-for result of early detection of disease-prone individuals would be the elimination of risk by appropriate treatment and the subsequent prevention or delay of disease. Whether or not such interventions can be successfully accomplished, particularly on a large-scale basis, must still be determined.

The program background, program goals, program status, and program plans are discussed in this section for each of the ten heart and blood vessel disease

program areas: arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, peripheral vascular disease, arrhythmias, heart failure and shock, congenital and rheumatic heart diseases, cardiomyopathies and infections of the heart, and circulatory assistance.

ARTERIOSCLEROSIS

Program Background

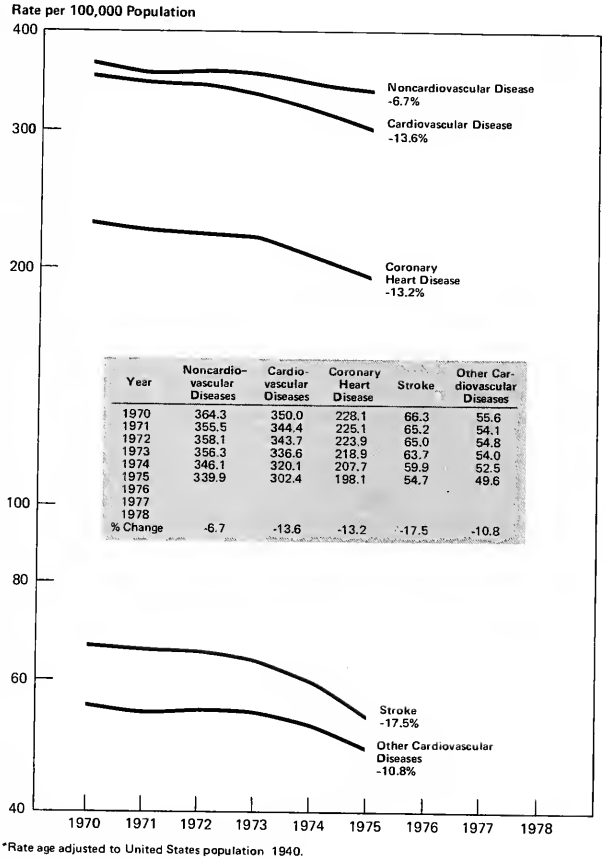
Arteriosclerosis literally means hardening of the arteries. In the type of arteriosclerosis responsible for the most serious clinical complications, the inner layer of the artery is characteristically thickened by soft fatty deposits called atheromas or atheromatous plaques. The blood vessel disease characterized by this type of deposit is often called atherosclerosis instead of arteriosclerosis. Atherosclerosis affects both large-sized and medium-sized arteries. It is generally a slow, progressive disease which may start in childhood but may produce no symptoms for 20 to 40 years or longer. Even in advanced stages atherosclerosis is sometimes discovered only at postmortem examination. During life, special X-ray examinations or sonarlike ultrasonic techniques are required for its diagnosis--except for lesions that contain calcium deposits which can be detected by routine X-ray techniques.

Epidemiologic studies indicate that atherosclerosis is related to certain life styles and habits, and to attitudes concerning health and treatment of chronic disease. Other factors, as yet undefined, are also involved in the genesis of this disease. The direct biological chain of events which produces the atherosclerotic lesion has not been completely established, and the reasons are not entirely understood for precipitation of its sequelae--a blocked artery, a heart attack, or a stroke.

High blood lipids, high blood pressure, obesity, diabetes, and stress are factors predisposing to atherosclerosis. Other factors that contribute to the susceptibility or resistance to this disease are the manner in which vascular cells control their metabolic and proliferative functions, the manner in which cells relate and interact in the vascular system, and the ways in which they adapt or react to defects in the body's control of its metabolic economy or circulation. Studies are under way to identify other risk factors that may exist in our environment or that may be produced by our life style.

Current understanding of the etiology of atherosclerosis has resulted in therapies that produce limited delay in the onset and progress of this disease, and future research results should increase this ability to postpone onset significantly.

Indeed, as indicated in Figure 6, the total death rate from cardiovascular diseases declined from 350.0 per 100,000 in 1970 to 302.4 in 1975, a decline of 13.6 percent, or 2.3 percent per year. At present, however, the available basic biomedical knowledge, the understanding of health attitudes, and the effectiveness of health education and behavior change are inadequate to enable us to prevent atherosclerosis completely. Furthermore, the serious clinical sequelae of atherosclerosis are difficult, if not impossible, to avoid. Consequently, the need remains for improved diagnosis, treatment, and rehabilitation as well as preventive measures.



Year	Noncardio-vascular Diseases	Cardio-vascular Diseases	Coronary Heart Disease	Stroke	Other Cardiovascular Diseases
1970	364.3	350.0	228.1	66.3	55.6
1971	355.5	344.4	225.1	65.2	54.1
1972	358.1	343.7	223.9	65.0	54.8
1973	356.3	336.6	218.9	63.7	54.0
1974	346.1	320.1	207.7	59.9	52.5
1975	339.9	302.4	198.1	54.7	49.6
1976					
1977					
1978					
% Change	-6.7	-13.6	-13.2	-17.5	-10.8

*Rate age adjusted to United States population 1940.

Figure 6. DEATH RATES* FOR CARDIOVASCULAR DISEASES (AND MAJOR COMPONENTS) AND NONCARDIOVASCULAR DISEASES, UNITED STATES, 1970-75

Atherosclerosis is not a precise disease entity but a constellation of disorders the expression of which is dominated by a number of complex pathological processes; hence, research on the disease involves many disciplines and approaches.

Program Goals

- The primary goal of the arteriosclerosis program is to prevent or postpone atherosclerotic disease and thereby reduce its morbidity and mortality. The program seeks a better understanding of the basic processes leading to this disease, and a better means of prevention, diagnosis, and treatment.

Program Status

Research interest in the mechanisms of lipid (fat) transport in the body has intensified in recent years. Certain lipid transport disorders characterized by abnormal elevations of blood lipids have been identified as a major (in many patients the major) risk factor in the development of atherosclerosis and of such of its lethal and crippling sequelae as heart attacks and strokes.

Cholesterol, a major component of all mammalian cell membranes, is vital to cell growth and survival; yet, excessive amounts of this sterol can also be lethal, as is evidenced by the cholesterol deposition in arterial cells that potentiates atherosclerosis. Thus, mammalian cells are faced with the dual problem of providing sufficient cholesterol for membrane growth and replenishment and at the same time of avoiding excessive accumulation of this insoluble substance. Mammalian cells utilize specific cell surface receptors to accomplish this dual task. This receptor, designated the low-density lipoprotein (LDL) receptor, binds the major cholesterol-carrying lipoprotein of plasma and thereby regulates the rate at which this lipoprotein transfers its cholesterol into the cell. The LDL receptor itself is under feedback regulation, and therefore, the amount of cholesterol that enters the cell is inversely proportional to the cellular content of cholesterol. Cultured cells obtain needed cholesterol by increasing their number of receptor molecules, and conversely, they protect themselves against an overaccumulation of this sterol by suppressing the synthesis of their LDL receptors. The complex interacting steps of this control are now being pieced together. There are indications that other cellular phenomena also regulate the metabolism of cholesterol and other lipids found in mammalian blood. Leukocytes (white blood cells) from patients with Type II heterozygous familial hypercholesterolemia (a severe lipid disorder) have an abnormally high efflux of cholesterol from their cells, suggesting that cellular binding of these substances is deficient in these patients.

Several key advances in blood lipid studies pertain to a class of blood proteins called apoproteins. These are natural detergents because they combine with fat soluble substances in the blood--cholesterol, triglycerides, and phospholipids--and convert them to water soluble complexes that can be readily transported in the blood plasma. Recently, scientists have determined the amino

acid sequence of five of these apoproteins and have identified the fragments of the dismembered apoprotein chain that combine with lipids. Apolipoprotein C-1 has now been totally synthesized from 57 amino acids by workers at the National Research and Demonstration Center at Baylor, Texas. This apoprotein occurs in the very low-density lipoproteins that transport fat in the blood. These results have led to a new concept of the apoprotein molecule as a unique two-faced, or amphipathic helical structure in which a large nonpolar face binds the fatty acid chains of the phospholipids, and a second polar face combines with its water soluble portion. Synthesis of model apoprotein pieces has strengthened this hypothesis.

The phenomena that occur during very early artery injury and the relationship of such injury to the production of atherogenic lesions are now being pieced together. The inner layer, or intima, of an artery is lined by a very thin single cell membrane, the endothelium. Denuding the intima of its endothelium stimulates the growth of smooth muscle cells, and these cells infiltrate into the arterial lining to form a diffuse plaque. The denuded intima is abnormally permeable to blood constituents such as proteins, and the original cellular proliferation can regress almost completely with time. However, on repeated injury rethickening or plaquing eventually occurs. In vivo and in vitro experiments suggest that platelet factors are essential for the smooth muscle cell proliferation following vessel injury. The latest sophisticated research techniques are being used to elucidate the exact role of blood platelets in thrombus formation and in atherogenesis, both in building the initial plaque after denudation of the inside of the blood vessel and in the subsequent thickening of the lesion.

As previously reported, regression of established atherosclerotic plaques can be produced in nonhuman primates. In recent studies, regression of early and moderately advanced lesions was produced by lowering serum cholesterol levels through the use of diets and drugs. This regression was not enhanced by, but was associated with, overall loss of cholesterol from the body. Evidence of plaque regression is now being sought in man. Indeed, a recent preliminary report states that plaque regression occurred in a small number of patients in whom elevated blood cholesterol and elevated blood pressure levels were lowered. As the complex interactions between endothelium, platelets, blood, and the blood vessel lining are further understood, specific pharmacologic agents for modifying plaque formation may become possible. For example, research on antiplatelet drugs is attempting to evaluate their possible therapeutic value in the prevention or reversal of atherogenesis.

Smoking is a major risk factor for atherosclerotic disease, especially heart attack. The Tobacco Working Group (TWG) of the National Cancer Institute (NCI) is attempting to develop less hazardous cigarettes and the NHLBI is working in liaison with this group.*

Nonhuman primates have been taught to smoke and inhale in a manner analogous to humans, thereby providing an animal model for the study of the pathogenicity of both conventional and new nontobacco cigarette substitutes.

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*See under *PROGRAM COORDINATION*, p. 157.

Suitable resource colonies of nonhuman primates have now been established for use in long-term studies of atherosclerosis and hypertension, and atherosclerotic modeling has begun. However, if the full potential of this model is to be realized, additional colonies are needed.

The Framingham Study has followed the health of the population (aged 30 to 60 years at the time of entry into the study) of Framingham, Massachusetts for 28 years. The approximately 5,200 original subjects comprised of men, women, and their off-spring have been given an in-depth medical exam every two years so that the present survivors (approximately 3,000) have received 14 such exams. The study has contributed much to our understanding of factors that predispose persons to heart attack and of the natural history of atherosclerosis and hypertension. The physical and mental capabilities of aging participants are being examined to determine how their functional status compares with their health examination data as accumulated over the previous 28 years. Analysis of the data on stroke, on brain function in old age, and on vascular disease with particular emphasis on cerebrovascular disease is being emphasized.

Atherosclerotic disease--cardiac, cerebral, or peripheral--is a major cause of morbidity and mortality among diabetics. Little is known about the mechanisms by which diabetes potentiates the development of atherosclerosis because most studies of atherosclerosis have excluded diabetics from the study population to avoid this complicating factor. A rare exception is the study of the evolution of cardiovascular disease in a subgroup of the Framingham population suffering from diabetes mellitus of sufficient severity to require insulin. These 148 men and 153 women had at least a doubled incidence of cardiovascular disease, and when such disease occurred, it was more likely to be fatal. Diabetes increased morbidity and mortality from all types of cardiovascular disease, and the increase was more pronounced in women than in men. The lower incidence of cardiovascular disease found in normal women prior to menopause compared to the incidence in men of similar age was absent in diabetic women. In men, diabetes imposed twice the risk of congestive heart failure; in diabetic women, the incidence of congestive heart failure was threefold greater than among nondiabetics.

Risk factors for atherosclerotic disease such as elevated blood lipid levels, hypertension, and obesity were present more frequently in diabetics, and the risk of cardiovascular disease associated with these factors was also increased. Epidemiological data reveal that when all other associated risk factors are taken into consideration, their presence explains only 20 to 30 percent of the increase in cardiovascular disease risk found in diabetics.

The report of the National Commission on Diabetes[8] referred to the seriousness of the atherosclerotic complications in diabetic subjects and called for more research to uncover the cardiovascular defect(s) involved. The National Heart, Lung, and Blood Institute (NHLBI) responded by releasing a Request for Applications (RFA) in this research area. The RFA resulted in over 160 grant applications of which 31 were judged of sufficient merit to be funded. Thus the Institute has successfully stimulated investigator-initiated research that will attempt to fill the knowledge gap in this important area.

The Lipid Research Clinics (LRCs) concentrate on the detection, prevalence, metabolism, and treatment of lipid disorders. There are 11 such clinics in

the United States, one in Canada, and one in Israel. There is also a formal program of collaboration with two clinics in the USSR. In the past five years, extensive programs of laboratory analysis, quality control, and education about lipid disorders have been developed by the LRCs. Nine LRCs in the United States together with the Canadian clinic have conducted standardized studies of the prevalence, determinants, and sequelae of hyperlipidemias. The populations which have been identified are black and white, young and old, rural and urban, and are employed in heavy and light industrial work; hence, they embrace a wide spectrum of society.

The basic LRC prevalence studies in the United States and Canada were completed by mid-1976 and an extensive analysis of the data has begun. Preliminary analysis of first-stage prevalence data indicates that premenopausal women on oral contraceptives have higher serum cholesterol and triglyceride levels than women not on such medication; and that a high proportion of hyperlipidemia in young women may be currently attributable to oral contraceptives. A further phase of these prevalence studies also includes determination of the prevalence of hyperlipidemia and the distribution of cholesterol and triglyceride values among first-degree relatives of selected probands, with and without demonstrably high, low, or intermediate lipid levels.

Two USSR clinics, one in Leningrad and one in Moscow, and the Lipid Research Clinic in Jerusalem, Israel, have been standardized* with LRCs in the United States and Canada. Prevalence studies of hyperlipidemia in populations in Moscow, Leningrad, and Jerusalem populations have been initiated. Preliminary analyses of data from a pilot prevalence study of USSR men suggest a significant elevation of serum high-density lipoproteins relative to US men. As this type of lipoprotein appears to be inversely correlated with risk of coronary heart disease, the characterization of such population subgroups and the elucidation of possible factors leading to this elevated high-density lipoprotein level is of paramount importance.

The dietary intake of selected nutrients in various regions and groups in the United States, Canada, Russia, and Israel is being ascertained. Dietary data in these studies are collected in accordance with protocols designed by the LRC program.

A Nutrition Coding Center (NCC) has been established to process comprehensive data on food composition. The effort to update and maintain food composition data is broad-based and involves Food and Drug Administration (FDA) and US Department of Agriculture (USDA) resources.**

Investigators have identified a number of distinct lipid-transport abnormalities. Each differs in clinical manifestations, in risk of producing secondary disorders, and in responsiveness to therapy. The increased blood lipids associated with these disorders may often be lowered by specific therapeutic diets with or without lipid-lowering drugs.

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*Standardization refers to both instrumentation and procedures and the checking of all results against blind controls.

**See under *PROGRAM COORDINATION*, pp. 153-54.

The Lipid Research Clinics Coronary Primary Prevention Trial (LRCs-CPPT) began in 1973 on the recommendation of the Arteriosclerosis Task Force. This seven-year study will test whether lowering cholesterol in hypercholesterolemic but otherwise healthy subjects (Type II hyperlipoproteinemia patients) will reduce or slow the development of premature coronary heart disease. Type II hyperlipoproteinemia is one of the most common of the blood lipid disorders and one of the most dangerous because of the associated high risk of premature atherosclerosis. The risk of death from coronary heart disease for patients with this disorder is 2.5 to 10 times higher than normal. Heart attacks are common in men under 50 with the Type II disorder.

Twelve LRCs, eleven in the United States and one in Canada, are cooperating in the LRCs-CPPT. Approximately 3,800 men between the ages of 35 and 59 have been recruited out of 500,000 men screened for this study. To qualify, subjects must have an elevated blood cholesterol level in the absence of severe hypertension, diabetes, endocrine disease, or other life-threatening disorders. They must be free of overt coronary heart disease or a history of heart ailments. The experimental group will receive a cholesterol-lowering diet plus the cholesterol-lowering drug, cholestyramine. The control group will receive the diet and a placebo (inactive pill).

Another clinical trial, the Multiple Risk Factor Intervention Trial (MRFIT), was begun in 1972, on the advice of the Arteriosclerosis Task Force. This six-year study aimed at our most important contemporary health problem, coronary heart disease, is the largest and most difficult primary prevention trial ever attempted by the NHLBI. Its goal is to prevent first heart attacks among men aged 35 to 57 years in the upper decile of the population at risk of death from coronary heart disease due to a combination of elevated serum cholesterol, elevated blood pressure, and cigarette smoking. Participants must have no preexisting clinical coronary heart disease. Half of those selected were randomly allocated to a special intervention program and half were referred to their usual source of medical care. The MRFIT trial involves 20 clinical centers across the country with a total of 12,866 participants. The primary recruitment phase of the study has been completed.

The intervention program consists of simultaneous dietary modification to lower blood lipids, drug therapy for high blood pressure, and counseling to discontinue or reduce smoking. An intensified intervention program has recently been adopted in an effort to improve compliance with therapy for hypertension and hypercholesterolemia. The effects of this special intervention program on the incidence of coronary heart disease (both nonfatal and fatal heart attacks), cardiovascular mortality, and total mortality from all causes are being monitored and the results are being analyzed. This trial will also greatly enhance our knowledge of effective methods for controlling major risk factors in free-living, subjectively healthy, coronary-prone, middle-aged American men, and of how to improve the living habits of these men and their immediate families.

A nutrition data collection program has been established which has standardized nutrition data collection procedures, as well as the training and certification of personnel at each clinic. Improved techniques of group education and individual instruction are being applied to produce changes in dietary patterns. New educational materials are being developed in coordination with

the Lipid Research Clinic Program. These materials have potential value for the community at large as well as for trial participants.

The report of the Task Force on Genetic Factors in Atherosclerotic Disease[9] has been published and widely distributed. The task force made broad-ranging recommendations to continue and increase studies of various aspects of genetics-oriented research of atherosclerosis. Specific topics singled out for study include: (1) genetic influences on plasma lipid and lipoprotein regulation, (2) a determination of the frequencies of monogenic, polygenic, and nongenetic forms of hyperlipidemia in various populations and cultures, (3) genetic components in diversity of response to treatment by diet or drugs, (4) an assessment of the significance of the possible monoclonal origin of the atherosclerosis lesion, and (5) a better definition of genetically determined biochemical and physiological correlates of behavior predisposing persons to coronary disease.

Thirteen Specialized Centers of Research (SCORs) have been established by the NHLBI in the area of atherosclerotic disease. A SCOR is an identifiable organizational unit within its institution with a central theme to which all individual projects relate. The specific purpose of these grant-supported centers is to advance basic knowledge and to develop the most effective methods of clinical management and prevention in the particular designated disease area. Therefore, the programs of a SCOR include basic, developmental or applied projects, and clinical investigations. The SCOR concept requires that each type of SCOR be a part of a national network of centers each addressing similar problem areas, and that there be close coordination among SCORs within these networks.

Recent activity in the 13 atherosclerosis SCORs has been focused on three major programmatic areas: (1) clinical studies of hyperlipidemia and/or vascular disease, (2) animal and tissue studies, and (3) basic laboratory investigations.

Although much new knowledge has accumulated in recent years, many challenging questions remain to be answered by arteriosclerotic research. More data on plaque formation at the cellular and subcellular, or organelle, levels remains the first priority. The recent research results reported above give great promise of rapid progress in this field. The difficult problem of identifying additional risk factors for these diseases remains a major challenge. However, atherosclerosis is a chronic, difficult-to-cure disease with late onset of symptoms. Therefore, specific, sensitive, noninvasive diagnostic instrumentation and techniques are urgently needed that can measure atherosclerotic plaques long before such symptoms are perceived by the patient. Recent improvements in diagnostic techniques promise a timely solution of this problem.

Society will not derive full benefit from the results of successful research programs in the pathogenesis, diagnosis, and treatment of atherosclerotic disease until these findings can be evaluated for efficacy and translated to the prevention and cure of disease in the community at large. Clinical trials and research on how best to accomplish prevention, education, control programs, and demonstration projects remain the final challenging steps.

Program Plans

Actions. The Institute plans to:

- Continue to emphasize studies of the causes and development of arteriosclerosis within existing and new research programs, Specialized Centers of Research, the National Research and Demonstration Centers, and Lipid Research Clinics.

- Expand research in cardiovascular disease in the diabetic patient and develop an appropriate research program in this area. The feasibility of a clinical trial of the therapy of juvenile diabetes in relation to vascular complications will be explored with the National Institute of Arthritis, Metabolism, and Digestive Diseases.

- Support epidemiologic and biochemical studies of the protective role of high-density lipoprotein in coronary heart disease. The determinants of high-density lipoprotein levels within the United States population will be studied through analysis of data on file in the Lipid Research Clinics' prevalence studies and through new initiatives.

- Encourage research on the pathogenic relationship of cigarette smoking to arteriosclerosis; continue efforts toward the efficient bioassay of the cardiovascular health risks of cigarettes modified to yield less tar, nicotine, and carbon monoxide; and attempt to assure that new cigarette formulations will be less hazardous to health.

- Expand research regarding the role of blood platelets and thrombosis in the development of arteriosclerosis.

- Implement recommendations of the Task Force on Genetic Factors in Atherosclerotic Disease, especially as they relate to understanding the genetics of hyperlipidemia and their potential for coronary heart disease prevention.

- Continue current genetic studies in the Lipid Research Clinics, Specialized Centers of Research, and Clinical Application and Prevention Programs.

- Encourage research on the identification and study of additional "risk factors" with the objective of elucidating all causes of premature coronary heart disease and other atherosclerotic complications. This effort will include basic, clinical, and epidemiologic research and will encourage studies of animal models.

- Encourage and continue the further development of noninvasive technology and methods for identifying and quantifying atherosclerotic plaques in humans.

- Evaluate current techniques for the diagnosis of hyperlipoproteinemia and other known risk factors and encourage the development of improvements in sensitivity, specificity, field applicability, and economy.

- Emphasize data analysis and publication of LRC prevalence studies and continue the Institute-supported nutrition coding center to code participants' dietary information and to maintain and update food composition tables and code books.

- Continue the already implemented Multiple Risk Factor Intervention Trial to determine whether a special intervention program will result in a significant reduction in mortality from coronary heart disease in men at above average risk of death from coronary heart disease because of elevated serum cholesterol, elevated diastolic blood pressure, and cigarette smoking.

- Continue intervention studies in high-risk subjects (e.g., Type II Primary Prevention Trial) to test whether lowering the concentration of lipids by selected means reduces cardiovascular morbidity and mortality.

- Continue the US-USSR cooperative study to define the prevalence of different types of hyperlipoproteinemia and their relationship to environmental factors--especially nutrition and other broadly defined cardiovascular risk factors.

- Expand current efforts to increase activity concerning the interrelationship between behavioral sciences and atherosclerosis. This will apply both to behavioral phenomena as possible etiologic factors and to behavioral considerations in relation to health education, awareness, and compliance with preventive and therapeutic measures.

- Evaluate and promote further the educational role of the Specialized Centers of Research, the National Research and Demonstration Centers, the Lipid Research Clinics, and the various clinical trials as training and information resources to the community in hyperlipidemia, nutrition, lipid metabolism, and lipid and lipoprotein analysis.

Schedule. The costs of the Multiple Risk Factor Intervention Trial and the Lipid Research Clinics Trial will peak in FY 77 and will remain stable, except for inflationary increases, through FY 81. Present support of Specialized Centers of Research is expected to decline somewhat in FY 77 and to show minor increments through FY 81. Expenditures in the specific area of diabetes and cardiovascular disease are expected to increase by 50 percent in FY 77 and to increase somewhat thereafter. New initiatives will be developed in atherogenesis, additional risk factor studies, and noninvasive diagnostic methods; these initiatives will be continued through FY 81.

HYPERTENSION

Program Background

Hypertension (high blood pressure) is not only the primary cause of more than 20,000 deaths in the United States each year, but also is thought to contribute to hundreds of thousands of deaths from heart attacks and strokes because it increases susceptibility to these events, which are the first and third causes of death in this country. Hypertension is a silent killer because in its early stages it produces no symptoms that require medical attention. Only after years of stress on the cardiovascular system does this disorder result in major complications such as stroke, heart attack, heart failure, kidney failure, and possibly atherosclerosis.

Although the prevalence rate rises steadily with age, hypertension also afflicts persons in the prime of their lives and in their most productive years. Nine out of ten cases of hypertension are "essential hypertension" (hypertension of unknown etiology) for which there is no known cure. It is more prevalent and also more severe in blacks than in whites. A 1971 to 1974 national survey estimated that 23 million persons in the United States, or about 18 percent of the adult population, have definitive hypertension (either a systolic blood pressure of more than 160 mmHg or a diastolic blood pressure of at least 95 mmHg). The survey also estimated that some 4 million persons who did not have definitive hypertension at the survey time had regularly used drugs to reduce their blood pressure over the previous six months before the survey. The survey also showed that 49 percent of the adult population with a hypertension problem were unaware of their disease, and of those who were aware, less than half were receiving adequate therapy (see Figure 4). Yet, once the disease is detected, it can usually be controlled, and treatment reduces the incidence of its sequelae. Present drug therapy, while effective, is not optimal because it requires life-long adherence, is expensive, has associated side effects, and must be individualized.

Program Goals

- The primary long-term goal of the hypertension research program is to understand the cause(s) of the disease and to eventually prevent its occurrence.

- A more immediate goal is to enhance the use of currently available therapy to control hypertension and prevent its complications.

Program Status

Hypertension results from a breakdown in the complex control system that maintains equilibrium between blood flow and the constricting and dilating forces affecting the arterial walls. In hypertension, the normal level of balance is shifted upward so that the blood is circulated in the arteries under higher pressure. This increased pressure may damage the blood vessels and the heart. The several complex systems known to regulate blood pressure--humoral, neural, central, and peripheral--are under extensive investigation. New and important

findings are continually being made of how the renin-angiotensin-aldosterone vasoconstrictor system regulates blood pressure. The kallikrein-kinin system and prostaglandins also are known to have a potent effect upon blood vessel dilation, and the physiological effects of these hormones are also under continuous investigation.

One of a series of events involved in blood pressure regulation is the release of the enzyme renin from the kidneys into the blood stream where it converts a plasma protein into angiotensin I, which in turn is converted by another enzyme into the potent pressor hormone, angiotensin II. Further progress has been made in our understanding of how this system works by using the angiotensin I converting-enzyme inhibitor (SQ 20,881) and the angiotensin II inhibitor, saralasin. The widespread use of these pharmacologic tools is uncovering the role of angiotensin II in hypertension. Hypertensive patients in whom the converting enzyme inhibitor and the angiotensin II antagonist do not lower blood pressure show a lowering of their blood pressure when placed on a low-sodium diet. These findings suggest that angiotensin plays an important role in essential hypertension and that changes in sodium balance may influence blood pressure, depending on the state of angiotensin activity.

An unusual reninlike enzyme of higher molecular weight than normal plasma renin was found last year. This new kidney-based substance, called "big renin," has now been extracted and purified. Current theories about the role of renin in blood pressure regulation are based on the belief that renin exists only in active form. The recent discovery of big renin* from hog kidney extracts indicates that the enzyme exists almost entirely as a larger molecule which is a less active or latent form of renin. This observation raises questions about how big renin is converted into the smaller active form, and what role this transformation may have in the blood pressure regulating process. Any one of several aspects of the conversion of the inactive renin to the active renin--such as the speed and site of the conversion as well as the biochemical mechanism of change--may play some role in the development of high blood pressure. In addition, an even larger molecule of renin (MW 140,000) called "big, big renin," has been isolated. The introduction of these new elements into the already complex renin-angiotensin-aldosterone system will likely open new approaches to the study of renin and blood pressure control.

Some hypertensive patients have elevated plasma renin levels while others do not. The search for new mineralocorticoids in patients with low-renin essential hypertension is also continuing. The importance of a mineralocorticoid, 18-OH-DOC, in some of these patients has been described. The metabolic pathways for synthesis of the hormone have been delineated and its hypertensive action has been demonstrated. A second new mineralocorticoid has been isolated from the urine of these patients and its structure is being determined. In parallel animal studies, increased mineralocorticoid activity has been observed in the urine of spontaneously hypertensive rats during the early stages of their disease. However, the nature of this material is uncertain.

*Molecular Weight (MW) 60,000 compared to normal renin MW 40,000.

Hypertension is one of the three major risk factors (along with cigarette smoking and hypercholesterolemia) for heart attack that are subject to intervention in the Multiple Risk Factor Intervention Trial.* Another study, the Hypertension Detection and Follow-up Program, is now in its third year. This study involves more than 10,940 participants in 14 communities and includes multiple ethnic, racial, and socioeconomic groups. The effectiveness of treating hypertension in reducing morbidity and mortality over all ranges of high blood pressure is being evaluated. A high degree of cooperation from the enrolled participants is being maintained, and the study is proceeding satisfactorily. Health education and behavioral research--as these may affect the individual's knowledge of hypertension, health attitudes towards it, and adherence to treatment--are also important aspects of the study.

Hypertension may also affect children, and in some cases, adult hypertension may have its antecedents in childhood. To delineate and understand better the significance of hypertension in childhood and young adult life, the Institute solicited applications for proposals in this specific area and subsequently awarded 16 grants for the study of the epidemiology of hypertension in the young. Because of the enthusiastic response by highly qualified investigators, it was possible for the Institute to initiate a more effective research program in this area.

The National Heart, Lung, and Blood Institute is collaborating with the Veterans Administration to test the therapeutic benefits of treating mild hypertension.**

A Task Force on Hypertension has been established by the Institute to advise on the research status, needs, and opportunities in biomedical research on hypertension. The 20-person task force, which met first in December 1975, has enlisted the help of more than 80 additional experts of varied backgrounds and interests. Subgroups were organized to review the needs and opportunities as they relate to hypertension in the following areas: local hemodynamics, systemic hemodynamics, renin-angiotensin-aldosterone, vascular smooth muscle, salt and water, neural control of the circulation, prostaglandins, hypertensive vascular disease, genetic hypertension, kallikrein-kinin, drug therapy, and pediatric hypertension. These subgroups will submit reports to the parent task force, which plans to issue a final report by the end of 1977. More than 100 persons are engaged in this task force; they are from all regions of the country and represent a wide range of institutions, disciplines, and experience. It is expected that the report of the task force will be a noteworthy contribution to hypertension research and will help to develop the Institute's plans in this important, rapidly advancing area for the next five years or more.

The routine measurement of blood pressure in man is simple, inexpensive, and noninvasive, but it provides only a single measurement at one point in time of a very labile parameter. Better instrumentation for continuous monitoring of blood pressure must be developed. There is a need for implantable microinstruments capable of continuous blood pressure measurement in small animals,

*See under *Arteriosclerosis*, p. 50.
**See under *PROGRAM COORDINATION*, p. 153.

and noninvasive devices which can continuously monitor free-living humans are also urgently needed.

On the recommendation of the National Heart, Lung, and Blood Advisory council in 1971, the NHLBI established a series of five Specialized Centers of Research in Hypertension.* Four hypertension SCORs are currently operating; their efforts are centered on the development and application of new knowledge for improved diagnosis, treatment, and prevention of all types of hypertension.

Program Plans

Actions. The Institute plans to:

- Continue to emphasize research on the etiology, pathogenesis, and epidemiology of hypertension
- Continue current trials to determine the effectiveness of antihypertensive therapy for the control of hypertensive disease
- Consider and assess, on the basis of experience with current trials such as the Hypertension Detection and Follow-up Program, the feasibility of definitive clinical trials of the therapy for treating mild hypertension (i.e., a diastolic pressure of 90 mmHg to 104 mmHg)
- Seek development of specific inhibitors to kinins, kallikreins, and prostaglandins to greatly improve the capability to study the physiological actions of these hormones
- Consider new and improved methods to assay various vasoactive substances such as prostaglandins, kinins, catecholamines, and their various metabolites
- Explore the potentiality and feasibility of research on the interaction of pressor substances with central nervous regulation of blood pressure
- Encourage the development of new instrumentation for all aspects of hypertension research
- Encourage studies on the epidemiology, etiology, pathogenesis, diagnosis, treatment, and prevention of hypertension in the young.

Schedule. Present programs will continue to receive emphasis. The Hypertension Detection and Follow-up Program will reach its maximum effort in FY 79, decrease substantially in FY 80, and enter its terminal year, in FY 81, at

*For SCOR concept, see p. 51.

approximately 10 percent of its FY 76 operating cost. The report and findings of the Task Force on Hypertension will be issued in FY 77. Specifically focused activities based on this report will be formulated and initiated in FY 77 and FY 78, and will be continued through FY 81.

CEREBROVASCULAR DISEASE

Program Background

Cerebrovascular disease is the basis for most strokes. It may be caused by high blood pressure and/or atherosclerosis of the vessels supplying the brain. Research in the areas of arteriosclerosis and hypertension therefore has direct applicability to cerebrovascular disease. Indeed, the effective control of either one may be expected to greatly reduce morbidity and mortality from stroke. However, it is also clear that the cerebrovascular bed poses its own particular problems in the pathogenesis of disease and in its diagnosis, treatment, and prevention.

While the National Heart, Lung, and Blood Institute is primarily responsible for the vascular antecedents of stroke, the National Institute for Neurological and Communicative Diseases and Stroke (NINCDS) is responsible for research on aspects of stroke dealing with brain injury and its effects.

Program Goals

- The goal of the program is to minimize the development of cerebrovascular disease through the study of its pathogenesis and etiology.

Program Status

The NHLBI and the NINCDS are coordinating their actions in an effort to enhance research on cerebrovascular disease. The NHLBI has supported research that has developed prototype diagnostic instruments using ultrasound to visualize atherosclerotic plaques and narrowing of the main blood vessels to the brain. This diagnostic technique does not require any invasion of the body and is painless, safe, and repeatable. It promises to be of great value when fully developed.

Investigators supported by the Institute have reported the experimental production of cerebrovascular atherosclerosis in nonhuman primates. This is the first experimental model of this disease to be described and should provide a useful new tool in its study. The Institute anticipates that its nonhuman primate resource, which was initiated last year to model chronic atherosclerosis and hypertension in these animals, will also produce valuable models for cerebrovascular disease research.

Cerebrovascular disease-related histories have been collected during LRC prevalence studies and are expected to contribute to the identification of possible risk factors. The Framingham Study has initiated research on brain function, cerebrovascular disease, and stroke among the participants of this

long-term study of the predisposition to, and the incidence and prevalence of, vascular and pulmonary disease.*

Relatively little research has been done on the specific pathogenetic changes of cerebrovascular disease induced by atherosclerosis and hypertension.

Moreover, there is a need for detailed assessment of cerebrovascular disease phenomena--pathological, functional, and pharmacological. A direct comparison with similar phenomena in the vascular beds of other parts of the body will help to elucidate the special properties and responses of this vascular bed.

The role of diabetes as a risk factor in the development of cerebrovascular disease deserves further study, as do the phenomena of platelet interactions, thrombosis, and embolism in this vascular bed. The international and geographic differences in the epidemiology of stroke require further clarification and interpretation. Because many of the phenomena of cerebrovascular disease are immediately germane to those of incipient, evolving, or completed stroke, the research issues often have an interdisciplinary character for neurologists and those in general cardiovascular research. The stimulation of interdisciplinary efforts is an important continuing challenge for both Institutes.

Program Plans

Actions. The Institute plans to:

- Continue basic etiologic and pathogenetic studies relevant to cerebrovascular disease
- Increase emphasis on animal models of cerebrovascular disease
- Continue selected epidemiologic studies dealing with the identification of environmental factors and personal attributes which predispose persons to increased risk of stroke and to vascular chronic brain injury
- Maintain surveillance of stroke end points in the clinical trials on arteriosclerosis and hypertension
- Expand the study of cerebrovascular phenomena proposed in the Framingham Study.*

Schedule. The development of animal models will continue as will surveillance of cerebrovascular events in cohorts already under study. The utilization of suitable animal models may be expected to expand pathogenetic research by FY 79.

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*See under *Arteriosclerosis*, p. 48.

CORONARY HEART DISEASE

Program Background

Coronary heart disease is the most common cause of death in the United States; the disease caused about 665,000 deaths in 1974, including approximately 159,000 among those under age 65. Based on a 10 percent sample, such deaths for 1975 are expected to decrease to 649,000 of which 154,000 are expected to occur in persons below the age of 65 years. Nonfatal heart attacks leave additional thousands with an impaired quality of life. Thus, it is especially appropriate that many programs of the Institute have been dedicated not only to understanding the cause of atherosclerosis and defining methods of effectively postponing or preventing this disease, but also to a better understanding of the clinical manifestations of coronary heart disease, heart attacks, sudden cardiac death, and angina, both stable and unstable.

It is reassuring to report that significant progress is being made in the understanding and treatment of coronary heart disease. The death rate from this disease decreased by 18 percent from 1968 to 1975. While the causes of this favorable change cannot be delineated, better techniques to recognize and manage the in-hospital manifestations of coronary heart disease are important. The Institute's Myocardial Infarction Research Units (MIRUs) played a role in the reduction of in-hospital mortality to approximately 15 to 20 percent. Unfortunately, however, the majority of patients who die of a myocardial infarction do so suddenly, and approximately 60 percent do not live long enough to be admitted to a hospital. Although we are seeing progress and some of the statistics are encouraging, we must continue to stress through research further improvements in the management of coronary artery disease. This seems especially true in those patients suffering heart failure, cardiovascular shock, and lethal arrhythmias.

Program Goals

The program goals are to:

- Develop information that will lead to improved diagnosis, prevention, therapy, rehabilitation, and understanding of the mechanisms resulting in symptomatic coronary disease
- Assess optimal medical therapy as well as the effectiveness of coronary artery surgery for the prevention of recurrent heart attacks
- Develop and assess emergency medical care suitable for heart attack victims
- Evaluate prophylactic treatment with drugs to prevent sudden cardiac death and heart attack in high-risk patients
- Develop and evaluate rehabilitation methods used to improve cardiovascular function, to reduce physical and psychosocial disability, and to enhance and prolong the effective life of patients with cardiovascular disease.

Program Status

In FY 75 in an attempt to focus and coordinate the varied research talents of major medical centers on specific identifiable programs of high priority, the Institute developed nine Ischemic Heart Disease Specialized Centers of Research.* Three SCORs supplemented and expanded the programs of nine Myocardial Infarction Research Units (MIRUs) which had been established in 1967 and 1968. The MIRU program had focused on only one aspect of coronary heart disease--clinical and basic research directly related to heart attacks. The Ischemic Heart Disease SCORs are now actively investigating the best means to assess and manage the various manifestations of acute and chronic ischemic heart disease. The interaction of basic and clinical scientists within each center has facilitated the rapid attainment of useful research results and has speeded the translation of these results into improved therapy. These specialized centers of research not only have greatly advanced our basic understanding of ischemic heart disease but also have made changes possible in the practical clinical management of patients with ischemic heart disease. For example, through the detailed study of clinical data, the typical hospital stay for cardiac patients may be shortened appreciably. Within the first week of hospitalization, it is now possible to identify a subset of patients with myocardial infarction who can be discharged within a week or ten days of admission without adversely influencing their prognosis.

The use of coronary artery bypass surgery to manage coronary heart disease is continuing to grow. Recent research suggests that at least in the small subset of coronary heart disease patients with severe narrowing of the left main coronary artery the procedure may prolong life as well as enhance the quality of life. The relatively low mortality resulting from coronary artery bypass surgery is continually becoming lower as experience with the technique grows. In the majority of suitable cases, this type of surgery produces relief from the symptoms of angina pectoris. However, the long-term benefits and the real effects upon the length of life are not yet established in most situations in which it is utilized. The operation is not without side effects, and it represents a substantial cost both to the individual and to society. Early results from a study of patients with unstable angina pectoris (a disease which simulates and may precede acute myocardial infarction) suggest that intensive medical management carries a prognosis equally favorable to emergency coronary bypass surgery. Under these circumstances, surgery appears to offer little advantage over intensive medical management.

A collaborative national effort, the Coronary Artery Surgery Trial (CAST), was undertaken to study in detail the indications for coronary artery bypass surgery. The true long-term benefits and indications for such surgery compared to appropriate medical management remain to be assessed. This study is now well established in 16 participating institutions, and extensive data from all patients undergoing coronary angiography at these institutions are being entered into a registry. The number of patients being entered into the registry is meeting expectations. A sharply defined subset of patients meeting well-defined clinical and coronary anatomic criteria is also being

*For SCOR concept, see p. 51.

randomized into two groups. The first group will receive surgical therapy, and the second group will receive medical treatment. In the past year, five new centers were added to the original 11 participating institutions in CAST to insure that an adequate number of patients would be available to broaden the base of the latter study.

The US-USSR cooperative study on the management of ischemic heart disease compares data from the Coronary Artery Surgery Trial of US patients managed both medically and surgically with patients in the USSR managed by a variety of medical-therapeutic regimens some of which are different from US therapeutic measures. Comparable data are being collected according to standardized protocols in both countries.*

Research on sudden cardiac death continues to provide a better understanding of this entity. However, much remains to be learned concerning the factors that convert chronic coronary heart disease into an acute heart attack. The phenomena underlining sudden cardiac death are still not completely understood. This lack of understanding presents a major challenge since approximately 60 percent of patients who die with coronary heart disease die of sudden cardiac death; that is, they die before hospitalization. Furthermore, for 20 percent of the sudden cardiac death victims, this is their first manifestation of coronary heart disease. Today, the wider, more effective implementation of emergency care systems is saving lives that otherwise would be lost to out-of-hospital deaths. Indeed, in one community of half a million, Seattle, Washington, approximately 100 lives are being saved annually by improved emergency care. Other lives are probably saved by these improved emergency care systems and the general tendency to bring patients under observation and treatment more quickly, before their heart muscle is irreversibly damaged.

The Institute has undertaken a program on sudden cardiac death and lethal arrhythmias. Several national conferences have been sponsored,[10] bringing together investigators working in this area to share in evaluation of their common goals and to help define new goals. Research has revealed that the terminal event that precipitates sudden cardiac death is usually ventricular fibrillation associated with increased irritability of the heart muscle. It may be possible to prevent the development of this fatal cardiac arrhythmia by chronic administration of antiarrhythmic agents. In patients at high risk, the results are promising in preliminary trials of prophylactic use of antiarrhythmic agents, particulary those drugs that block the beta-adrenergic system. A definitive trial will be undertaken to assess the efficacy of one of the antiarrhythmic drugs currently available in the United States. The clues that enable recognition of those at high risk must be further defined to enable identification of those patients in whom such prophylactic therapy could be a reasonable undertaking. Many other facets of the precipitants of sudden cardiac death or the conditions that convert chronic coronary heart disease into an acute catastrophic illness are not clearly understood. The role of the autonomic nervous system and other possible psychophysiologic factors need further investigation.

*See under *PROGRAM COORDINATION*, p. 161.

In an attempt to reduce the recurrence of reinfarctions, the Institute has initiated the Aspirin Myocardial Infarction Study (AMIS). The promising results of earlier pilot studies have led to the undertaking of a definitive, large-scale clinical trial involving over 4,500 participants to determine whether the regular ingestion of aspirin reduces the incidence of recurrent myocardial infarction. Patient recruitment for this trial was completed early in the summer of 1976, and follow-up studies on the trial participants will continue over the next three years.

Cardiac disease is the cause of death for 80 percent of those afflicted with diabetes. However, some studies of coronary heart disease, in an effort to maintain as homogeneous a population as possible, have sought to exclude patients with such complicating illnesses as diabetes. The Institute has launched a specific research effort to study the cardiovascular problem of the diabetic because of the importance of cardiac disease to the diabetic and the magnitude of diabetes as a public health problem.*

Well-directed rehabilitation has been reported to give the patient with cardiac disease an improved sense of well-being, an enhanced work capacity, and a better integration into family and society. Although a variety of rehabilitation programs have been undertaken, a better scientific basis for such rehabilitation is needed. Therefore, research more comprehensive in scope is required in the area of cardiac rehabilitation. Topics that require further investigation include: (1) the role of the central and peripheral mechanisms that control cardiovascular responses to a given set of physical or emotional conditions, (2) the identification by invasive or noninvasive methods of patients likely to benefit from physiological reconditioning procedures, (3) the psychosocial determinants required for effective rehabilitation, and (4) comparative studies of the effects of different intervention techniques on patient adherence to therapy.

In summary, improved diagnostic methods to detect coronary heart disease, assess its severity, and judge its prognosis have been developed, and these have brought about a substantial improvement in our ability to diagnose and manage such disease. Both the limits and the benefits of exercise-stress testing are being increasingly well defined. The more complex procedures include: (1) improved methods of cardiac catheterization, (2) radiographic techniques which may obviate or reduce the need for a contrast medium, (3) radioisotopic techniques that can detect and possibly quantify the size and site of infarcted myocardium as well as assess the fraction of blood ejected from the ventricle, and (4) radioimmunoassay techniques that can detect a variety of chemical changes associated with acute myocardial disease. However, at present these new techniques are not being used with sufficient uniformity and their comparative merits have not been adequately assessed. More research is required to insure that the results of these new and powerful tests are interpreted in a manner that leads to an appreciation of their limitations as well as of their benefits. Program plans for the future are designed to refine the significant developments accomplished to date. And as more basic and clinical data concerning ischemic heart disease become available, the Institute will insure rapid therapeutic application of this knowledge.

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*See under *Arteriosclerosis*, p. 48.

Program Plans

Actions. The Institute plans to:

- Continue to support the recently established nine Specialized Centers of Research focused on the unsolved problems of coronary heart disease.

- Continue the collaborative Coronary Artery Surgery Trial to determine the indications for, and the long-term effects of, coronary artery surgery in the management of coronary heart disease.

- Promote prospective and retrospective studies to elucidate the mechanisms and factors that precipitate acute coronary events and to determine the characteristics of individuals at high risk for these events. Special attention will be given to the survivors of acute cardiac arrest or ventricular fibrillation with particular reference to the state of their coronary arteries, conduction system, and heart muscle.

- Promote studies on the prodromata of acute coronary events and of patients' physiological reactions and coping behavior in this setting--including the psychological factors that lead to patient delay in seeking treatment--to enable earlier diagnosis and treatment.

- Continue to develop and test new techniques of emergency cardiovascular diagnosis and therapy.

- Design and prepare for the implementation of controlled trials of chronically administered antiarrhythmic drugs in patients at high risk of myocardial infarction or sudden cardiac death.

- Expand and accelerate critical studies to evaluate both the strengths and limitations of coronary arteriography, radioisotopic imaging of the heart chambers and myocardium, exercise electrocardiography, and echocardiography in the study of patients with coronary disease.

- Foster the development and assessment of techniques for the early and accurate detection of persons with unrecognized coronary heart disease.

- Stimulate controlled studies of the effect of various programs of medical treatments on survival, incidence of acute myocardial infarction, and functional capacity of persons with coronary heart disease.

- Promote studies on coronary heart disease in the diabetic patient.

- Continue the clinical trial to assess the possible efficacy of regular aspirin ingestion in decreasing the incidence of recurrent myocardial infarction.

- Stimulate research on rehabilitation of physiological and psychosocial functions in cardiac patients.

- Continue the US-USSR cooperative study on the management of ischemic heart disease by medical and surgical techniques.

- Continue to implement the US-USSR cooperative program on the prevention of sudden cardiac death.

Schedule. The Specialized Centers of Research on Ischemic Heart Disease will be continued. Competitive expansion of the program on methods of quantifying the size and extent of ischemic myocardium is anticipated in FY 77. Chronic antiarrhythmic prophylactic therapy against sudden cardiac death will be designed and will enter the pilot phase possibly by the end of FY 77. A program announcement on rehabilitation in cardiac disease is under consideration and may be issued in FY 77 or FY 78. Workshops and symposia to assess various diagnostic techniques will be sponsored in FY 77. Basic and clinical research on all aspects of coronary heart disease will continue over the next five years.

PERIPHERAL VASCULAR DISEASES

Program Background

Narrowing of the arteries that perfuse the extremities and insufficiency of the venous return from the extremities cause considerable suffering and disability. Techniques have been developed to replace and bypass diseased arteries with vascular or prosthetic grafts. However, peripheral arterial disease, peripheral venous disease, and disorders of the lymphatics have been the focus of only limited research efforts in past years. Although revascularization techniques are widely applied, particularly for medium-sized and large-sized arteries, and a variety of prosthetic grafts are implanted, long-term results of these procedures and the fate of the prostheses require more documentation.

Program Goals

- The goals of the program are to improve diagnosis, therapy, and rehabilitation, and to improve understanding of the mechanism causing peripheral arterial, venous, and lymphatic diseases.

Program Status

Diagnostic methods to assess the severity of peripheral arterial disease have improved, particularly with the advent of new ultrasound, radioisotopic, and radiographic techniques. The cause, diagnosis, and prevention of thrombi in peripheral veins are becoming better understood. Early and sensitive indicators of thrombosis have been developed, and considerable interest and discussion

have been aroused as a result of the use of prophylactic low-dose heparin therapy to prevent thrombosis in high-risk patients.*

Despite the important advances in the diagnosis, prevention, and management of peripheral venous diseases such as thrombophlebitis, these warrant further activity. Also, perpheral arterial disease in the diabetic needs special study.

As a continuation of earlier work with large peripheral vessels, considerable interest has now focused on reconstructive procedures for smaller peripheral arteries and on the development of better prosthetic grafts for this purpose. The long-term fate of these prosthetic grafts is not yet known. The whole area of peripheral vascular disease requires further study. Better methods must be developed for early diagnosis of peripheral vascular diseases for more effective medical management, and for the extension of surgical therapy to small vessels. Understanding the basic cause of the disease is most important. This requires further study of the role of neural control of vascular tone, the mechanisms of action of smooth muscle, the pathogenesis of peripheral atherosclerosis, the mechanism of vascular disease in the diabetic, and the importance and significance of risk factors.

Program Plans

Actions. The Institute plans to:

- Further encourage clinical, laboratory, and epidemiological research into the causes, diagnosis, and treatment of diseases of the peripheral arteries, veins, and lymphatics
- Encourage studies of the long-term results of vascular replacement operations, including the fate of implanted prostheses
- Encourage investigation leading to the development of effective small diameter vascular replacements
- Promote studies of the peripheral arterial disease problems in the diabetic patient
- Encourage research on the diagnosis, prevention, and management of deep vein thrombosis and its sequelae
- Implement related programs described in the section on Arteriosclerosis.

Schedule. In FY 77, the Institute will sponsor a Symposium on Vascular Grafts emphasizing the current status and future trends with particular attention on small vessel grafts. In FY 77, grant applications will be sought on the general problem of diabetes, including specific reference to the problems of peripheral arterial disease in the diabetic. Basic and especially clinical investigation

*See under *Venous Thrombosis*, p. 100.

will develop in this general field over the coming five years with particular attention to diagnostic methods, better vascular grafting techniques, and long-term follow-up of currently used grafts.

ARRHYTHMIAS

Program Background

Arrhythmias and other electrical disturbances of the heart cause important symptoms and aggravate many forms of heart disease. They are frequently the immediate cause of heart failure and death. Identification of arrhythmias that carry a high risk of sudden cardiac death is fundamental to the development of preventive measures.

Program Goals

- A major goal is to develop and evaluate methods leading to the understanding and prevention of arrhythmias, particularly those which may cause sudden death.

- Another goal of the program is to continue to improve currently available methods to prevent, diagnose, and manage arrhythmias and other electrical disturbances of the heart.

Program Status

The electrophysiological mechanisms underlying arrhythmias are becoming increasingly better understood. Additional studies of the so-called "slow response" have been undertaken, including the demonstration that digitalis-induced ectopic rhythms may involve the same or similar calcium currents. These studies have led to investigation of calcium current antagonists in experimental models and in clinical cases of ventricular arrhythmias.

Studies of the role of the autonomic nervous system in the genesis of abnormal rhythms may lead to the development of more effective therapeutic interventions. Patterns of conduction and disease-associated disturbances and the mapping of abnormal pathways of electrical conduction have yielded improved understanding of the underlying causes of arrhythmias. This understanding has led to a more specific therapy for certain forms of rhythm disorders.

The current interpretations of the analysis of normal and abnormal cardiac rhythms and the influence of drugs on these rhythms must be assessed by quantitative analysis of extensive electrocardiographic recordings. Progress has been made toward performing this task automatically, rapidly, and quantitatively by computer. Further research with these methods is underway. Computer arrhythmia analysis systems have become more widely used in clinical studies. These systems have now emerged from the developmental stage and are being applied to the analysis of arrhythmias in both the coronary care unit and in ambulatory patient studies. Although a number of systems are now in routine use, comparison among them is difficult because no generally acceptable standard exists. Data from such automated systems are being used to monitor the effects of various drug regimens, to study the results of coronary artery

surgery upon arrhythmias, and to study the relationship of arrhythmias to coronary artery disease and sudden cardiac death.

Precise analysis is an essential part of the clinical evaluation of new antiarrhythmic agents for chronic use, but the major end point of the evaluation must be an improvement in long-term mortality. A variety of agents which modify the electrophysiological properties of the heart are now available and new ones are being evaluated. Pilot studies, however, have frequently demonstrated the serious side effects which are likely to limit the effectiveness of many of these drugs for use in chronic antiarrhythmic prophylaxis. On the other hand, very promising studies have also been reported with agents which suppress the beta-adrenergic system and thereby diminish the propensity for ventricular arrhythmias.

A better understanding of the electrical behavior of the diseased heart is essential for better therapy. For example, we still do not know whether idioventricular activity accompanying coronary artery disease is due to reentry or to ectopic pacemaker activity. In some early trials, beta-adrenergic blockers have yielded attractive preliminary results as prophylactic antiarrhythmic therapy against sudden cardiac death in those who have survived a heart attack and are therefore at high risk. These studies are not conclusive, and the overall cost and benefit of this antiarrhythmic therapy must be assessed. It is well established that premature ventricular contractions may in special circumstances precipitate bouts of self-sustained tachycardia or even fibrillation. It follows that drugs that could prevent the triggering event might prevent the more dangerous sequelae, even if those drugs cannot abolish the self-sustained arrhythmia once it is established. It is necessary to learn much more about these natural events. Also, for use in clinical studies, more highly automated and standardized systems need to be developed not only to quantify the frequency of premature ventricular contractions, but also to assess other indices of the severity of arrhythmias.*

Program Plans

Actions. The Institute plans to:

- Expand current studies on the prevention of arrhythmias. Studies will focus on the electrophysiology and therapy of rhythm disturbances associated with inadequate blood supply to heart muscle and on clinical studies to identify chronic or intermittent disturbances of heart rhythm which are indicative of an increased risk of sudden death.

- Augment the development of standardized automated quantitative techniques to analyze electrocardiographic rhythm signals in order to facilitate clinical investigation of arrhythmias and the automated detection of arrhythmias.

*See discussion of antiarrhythmic agents and sudden death under *Coronary Heart Disease*, pp. 62-63.

- Continue to support research on, and development of, new antiarrhythmic agents in the search for suitable drugs for long-term prophylaxis in high-risk patients.

Schedule. A new and expanded program on arrhythmias will emphasize those arrhythmias suspected of causing sudden cardiac death. In FY 77, further targeted efforts are planned in research on the control of lethal arrhythmias associated with ischemic heart disease including the planning and initial testing of clinical trials to assess the possible beneficial effects of chronic antiarrhythmic (beta-adrenergic blocking) therapy in high-risk patients. Basic and clinical research on cardiac arrhythmias will continue for at least the next five years.

HEART FAILURE AND SHOCK

Program Background

Shock can result from various causes. Cardiogenic shock, the type of shock caused by extensive heart muscle damage during heart attack, results in a mortality of 85 percent or more. Heart failure can result from various forms of heart disease. One acute, severe form that may be associated with heart attack results in a death rate of about 50 percent. Chronic heart failure is a disabling malady affecting approximately 4 million persons in the United States. The disabling effects range in severity from milder forms which can be controlled by drug therapy to more severe types which completely incapacitate the patient. Elucidation of the basic biological processes underlying cardiac function is required for a complete understanding of these disorders and to develop methods to improve diagnosis, prevention, and treatment. The basic biological processes that are essential if the failing heart is to perform its workload require further investigation. These include energy production and utilization, turnover of cellular components, and the contractile process.

Program Goals

The program goals are to:

- Improve the understanding and thereby the management of heart failure and shock
- Obtain an in-depth understanding of normal cardiac function as a basis for understanding the mechanism of heart failure
- Understand the pathological processes that lead to failure of cell function or to cell death in heart muscle so that by enhancing survival of such damaged heart muscle, heart failure will be lessened or prevented following heart attack
- Develop more satisfactory means of quantifying in patients the extent of heart muscle which is inadequately perfused with arterial blood or which has undergone irreversible damage

- Develop specific new pharmacological agents to improve the function of failing heart muscle in humans.

Program Status

Significant progress has been made both in the basic science laboratory and in the clinical setting. The complex calcium-protein interactions in cellular membranes and subcellular organelles of the heart muscle are better understood. Derangements of these interactions are underlying causes of heart disease. Various, newly developed calcium-active agents can favorably influence these changed interactions. This ability to understand and correct depressed contractility in affected heart muscle may be one of the most important steps in the eventual control of clinical heart failure and shock.

Development of optimal procedures to prevent irreversible damage to heart muscle depends upon identification of the critical processes linking cell death to defects in energy production and utilization, and to destruction of cell components. The amount of irreversible cell damage is not predetermined at the onset of heart attack. There is a significant amount of muscle that is jeopardized but is still viable for six or more hours. Current research has identified several promising means to promote the recovery of these potentially reversibly damaged cells.

Much is now known concerning energy production in heart muscle deprived of an adequate arterial blood supply. Although this tissue becomes energy depleted, the usual compensating energy production through utilization of glucose is impaired. By contrast, in energy-poor heart muscle induced by reduction of blood oxygen content with maintenance of coronary flow, energy production from glucose is markedly increased. Therefore, impaired energy production in ischemic muscle appears to be due to reduced washout of lactic acid and other acidic products of metabolism rather than to the decreased oxygen tension of the blood perfusing the cardiac cells.

Two major problems in clinical evaluation and control of heart failure and shock have been the accurate determination of that portion of total heart muscle which is dead or dying, and whether the therapy employed is affecting the diseased rather than the normal muscle. Adequate methods are available to quantify the process in experimental animals, and in the past year, noninvasive methods of testing in man have been improved. However, additional information is needed before the amounts of heart muscle affected and the changes of diseased muscle under specific therapies can be determined. Promising methods for quantifying dead and dying muscle include sequential mapping of the electrical signals from the heart as they appear on the chest wall and visualization of impaired or normal heart muscle by radioisotopic techniques. In addition, new ultrasonic equipment with multiple-focused signals can signal the inner and outer surfaces of the heart and valves with excellent clarity thereby allowing some types of pathology to be identified. Measurement of the release of enzymes by dying heart muscle offers another approach to quantification of the volume of dead muscle. These techniques are vital in order to develop and evaluate various therapies designed to control cardiac muscle damage and to impede the subsequent risk of heart failure and shock. A range of pharmacologic agents as well as mechanical circulatory assist devices have proved beneficial to patients with heart failure or shock.

Program Plans

Actions. The Institute plans to:

- Develop methods capable of minimizing the extent of heart muscle damage following heart attack by enlarging biochemical, physiologic, pathologic, and pharmacologic studies of the fundamental processes involved. These studies, both laboratory and clinical, will focus on the cellular factors leading to death of heart muscle.

- Establish clinical studies, contingent upon the success of current pilot studies, to assess the therapeutic efficacy of promising techniques used to minimize the extent of heart muscle damage following a heart attack. These studies will include follow-up of patient survival and the degree of cardiac disability produced.

- Expand the program for quantifying the extent of heart muscle which is inadequately perfused or which has undergone irreversible damage.

- Continue the US-USSR cooperative program on myocardial metabolism.

Schedule. Continuing and new actions related to cardiac failure and shock will emphasize the pathophysiology of ischemic myocardium and methods of quantifying this condition, as well as directing attention to the systemic responses to heart failure and shock. During FY 77, initiatives will be taken to expand studies aimed at quantification of infarct size. Contingent upon developments in pilot studies, clinical studies to assess these therapeutic interventions may be begun. In the period FY 78 through FY 81, additional investigations of the biochemical and physiological bases of myocardial infarction will be undertaken.

CONGENITAL AND RHEUMATIC HEART DISEASE

Program Background

Congenital and rheumatic heart diseases are serious disorders of childhood, adolescence, and adulthood which impair the quality of life and often cause premature death. For the most part, the causes of cardiac defects in the developing fetus are not known. For some forms, early detection is of paramount importance. Death in the neonatal period is still all too common because of lack of recognition and adequate therapy. For a number of forms of congenital heart disease for which surgical therapy seems effective, the long-term post-operative outcome is not sufficiently known.

Rheumatic heart disease is an immunological disturbance that frequently occurs years after initial rheumatic fever and prior streptococcal infection. The control of streptococcal infection through the prophylactic use of antibiotics has decreased the impact of the disease without eradicating it. A better

understanding of the immunological problems and their control would aid in the identification of susceptible patients. Such knowledge would also improve the success of cardiac transplantation and aid in the prevention or treatment of cardiomyopathies and possibly other forms of heart disease.

Program Goals

The program goals are to:

- Understand the causes of congenital heart disease, to improve its diagnosis and therapy, to assess the long-term effects of therapy, and to rehabilitate patients with the disease.

- Obtain a better understanding of the immunological problems associated with rheumatic heart disease.

Program Status

Results of in vivo animal experiments, which have elucidated the normal developmental process of the cardiovascular system, have led to a much better understanding of human fetal development. These experimental findings have suggested possible mechanisms by which certain congenital lesions are produced. Such mechanisms include blood flow disturbances in the embryonic heart which result in the underdevelopment of certain areas. The interaction of the developing heart with other systems is being evaluated with respect to such abnormalities as patent ductus arteriosus and its dilation and constriction. The use of prostaglandin inhibitors may have important favorable effects on the early mortality of newborn infants with respiratory distress syndrome or with lesions resulting in severe obstruction to pulmonary blood flow.

Earlier diagnosis, particularly useful in the neonatal period, has been aided by the use of echocardiography alone and in combination with other techniques. Pediatric intensive care units have led to better preoperative and postoperative care with subsequent lowering of mortality. Early diagnosis in utero is possible in some forms of congenital heart disease associated with chromosomal abnormalities.

A better understanding of both the normal and abnormal development of the cardiovascular system is essential if congenital heart disease is to be prevented. The roles of maternal infection and toxic exposures during pregnancy are particularly relevant. The emphasis on diagnosis, therapy, and rehabilitation of congenital heart disease patients must be increasingly focused on the newborn. Particular attention must be paid to measures that will assure the first few critical hours of life.

Animal models are being developed as analogs for congenital heart disease in man. Strains of dogs with a variety of defects are becoming more readily available for study. Defects in these strains include pulmonic, aortic, and subaortic stenosis, patent ductus arteriosus, and septal defects. Physiologic, embryologic, histopathologic, biochemical, and statistical studies are proceeding to analyze the genetic and the mechanistic contributions to these lesions.

Additional data on the changing incidence of congenital heart disease in response to changing genetic input, as well as of toxic agents and drug effects, may lead to important clues that will help to prevent congenital heart disease in a portion of the population. From this type of information, genetic counseling may become more firmly based in the prevention of congenital and some other forms of heart disease.

New surgical techniques which allow earlier interventions to correct many congenital defects have steadily decreased mortality. An assessment of the result of surgical repairs in children with congenital heart disease, whether done in infancy or in older children is important. Long-term follow-up of the physiologic effects of surgery and of the quality of life of these patients is essential. Prevention of cardiovascular disease in children and in adults is dependent upon knowledge gained from the study of children.

We must learn to recognize the group at risk of developing cardiomyopathies. The problems of multifactorial etiology plus unknown immunological reaction leave a wide area of investigation. At best, until the basic abnormalities of these diseases are understood, treatment and/or prevention remain limited.

Closely related programs which deal with the management of congenital heart diseases in the newborn are discussed in the section on Prevention, Education, and Control.

Program Plans

Actions. The Institute plans to:

- Establish a task force to evaluate heart disease in children
- Consider the establishment of Specialized Centers of Research on Congenital Heart Disease at two to four locations, emphasizing in these centers research topics such as cardiovascular development, epidemiology, improved diagnostic techniques, and better therapy with particular emphasis on the newborn
- Consider the feasibility of establishing a registry of post-operative patients who have undergone repair of congenital cardiac defects to assess the physiological and functional results on a long-term basis
- Encourage studies of immunological problems in heart disease and their management--specifically in relation to rheumatic heart disease, transplantation, and cardiomyopathies
- Continue research to define the optimal duration of prophylactic therapy aimed at the prevention of streptococcal infections and rheumatic fever
- Continue the US-USSR cooperative study on congenital heart disease.

Schedule. Over the next five years there will be continued emphasis on the etiology of congenital and rheumatic heart diseases. In the area of congenital

heart disease, there will be an increasing clinical emphasis on the neonatal period and on the long-term follow-up of postoperative patients.

CARDIOMYOPATHIES AND INFECTIONS OF THE HEART

Program Background

Cardiomyopathies and infections of the heart may cause enlargement of the heart, heart failure, irregularities of heart rhythm, and occasionally, sudden death. These conditions clearly cause significant cardiac morbidity and mortality. Cardiomyopathies are being recognized more often, either as a result of an increased incidence and/or because of more precise diagnoses.

Most cardiomyopathies are of an unknown cause (idiopathic cardiomyopathies); with some, the causative agent is known, and with others, there may be a hereditary predisposition. Our ability to correct the abnormal process depends upon our ability to determine the factors which cause this group of heart diseases.

Program Goals

- The goals of the program are to improve the diagnosis of cardiomyopathies and to learn the etiology of the various cardiomyopathies and infections of the heart. Improved understanding of the causes of these diseases will lead to better treatment and perhaps to the prevention of this form of heart disease.

Program Status

Cardiomyopathies are being recognized with increasing frequency with the aid of more sophisticated diagnostic techniques such as the echocardiogram and with the description and recognition of new clinical syndromes. Often these cardiomyopathies are subclinical, presenting no symptoms, and are detectable only upon careful examination. On the other hand, they may progress sometimes suddenly and unexpectedly to serious heart disease and sudden death. Such disease may range from conditions involving asymmetrical hypertrophy of the heart muscle to other disorders detectable through their electrophysiologic effects. Some cardiomyopathies have important familial predisposition.

Toxic substances are increasingly recognized as a cause of cardiomyopathies. The importance of alcoholic cardiomyopathy is becoming increasingly apparent. However, the causes of many other cases of cardiomyopathy and inflammatory conditions of the heart are unknown. The role of infection, particularly by viruses, is clearly an important factor in the etiology of this group of diseases.

Bacterial endocarditis--the bacterial infection on the inner surface of the heart--as a complication of rheumatic or congenital heart disease is now uncommon because antibiotics are used at the time of dental extractions and in other high-risk situations. However, the presence of prosthetic devices, such as artificial heart valves, creates a nidus around which bacterial infection can more readily grow and which is more resistant to eradication by antibiotics.

Moreover, massive chemotherapy and immunosuppression depress the body's normal defenses against foreign cells. The use of these therapies for certain diseases has led to the production of endocarditis by organisms that are non-pathogenic under normal conditions.

Since cardiomyopathies stem from a variety of causes, research efforts must be broadly based and involve multiple disciplines. Cellular and subcellular biochemical, immunological, and ultrastructural studies offer opportunities to improve our understanding of these problems. The role of toxic substances such as drugs and alcohol and of viral infections and genetic disorders needs to be further investigated. Better diagnostic and therapeutic approaches to these diseases must be developed. Armed with this knowledge, studies of their etiology and treatment will become more precise and efficient.

Program Plans

Actions. The Institute plans to:

- Continue attempts to identify and characterize cardiomyopathies in man with the aim of defining the mechanisms of these disorders.

- Consider the possiblity of establishing one or two centers for the study of cardiomyopathies in order to provide a critical mass of patients for detailed prospective and retrospective etiologic studies of these conditions. Specifically, the Institute would plan to focus attention on studies of the etiologies of cardiomyopathies and infections of the heart, emphasizing epidemiologic methods, viral and immunologic research, the development and utilization of animal models, and the determinations of mechanisms of myocardial damage by application of biochemical, physiologic, pathologic, physical, and pharmacologic techniques.*

Schedule. As this field is developed, continuing and new actions with initial emphasis on the cause of cardiomyopathies will permit an increase in activity with progressive increases in funding through FY 81.

CIRCULATORY ASSISTANCE

Program Background

Management of acute and chronic cardiac insufficiency and shock by available drugs, while of increasing effectiveness, still leaves a substantial number of patients with fatally compromised heart function. It is now possible to support by mechanical means a portion of the pumping function of the heart. In this way, the workload of the heart is relieved while adequate perfusion

*See under *Congenital and Rheumatic Heart Disease,* pp. 72-73.

of blood throughout the body is maintained. Currently available techniques have been used in experimental animals for several months.

There is still much to be learned in order to assess and quantify the degree of circulatory impairment which justifies the application of mechanical assist devices, the extent of relief that can be provided by such therapy, and the limitations imposed by the nature of the underlying disease. New insights into basic physiological phenomena and disease states will be obtained through the use of new technology as this is perfected. Then by an iterative process applying these new insights, still better technology will be developed to control heart disease.

Program Goals

- A major goal of the program is to develop and evaluate left ventricular assist devices and eventually total heart replacement systems capable of supporting or taking over the pumping function of the failing heart. This involves the development and evaluation of the materials needed for the construction of pump chambers, valves, blood conduits, and other kinds of implantable prosthetic devices.

- A second goal of the program is to assess the therapeutic effectiveness of cardiac assist procedures and devices, and to separate those patients in whom a temporary assist will be effective because healing can be anticipated from those patients who will require a permanent assist system or who cannot be helped by the mechanical approach.

Program Status

There is increasing clinical evidence to validate the use of cardiac assistance in patients with pharmacologically intractable heart failure following cardiac surgery. In experimental animals, cardiac assist devices designed to reduce the load on the left ventricle have reversed heart failure and shock. In some laboratories animals with total heart implant are now surviving for months without anticoagulant therapy. In these experiments the blood pumps are activated pneumatically from outside the body.

Electrical and thermal engines designed for implantation within the body have been reduced in size. Their efficiency in converting electrical or chemical energy into mechanical energy has been improved. At the same time, better pump and valve designs have reduced actual power requirements for partial and total heart replacement devices. Several elastomers combine the ruggedness expected of a flexing pump component with reasonably good blood compatability. Improved pump and valve design, greater understanding of the cardiac assist mechanisms, better characterization of biocompatible surfaces, and advances in anticoagulant regimens have all contributed to the higher rate and to the longer term of survival obtained in experimental animals supported by prosthetic cardiac implants.

Several new biomaterials have been synthesized, including epidermally cell-lined polymer conduits. Studies are continuing on candidate polymer materials for blood pump lining, emphasizing long-term flex life, mechanical properties,

toxicity, sterilizability, characterization, and biocompatibility of these polymers while measuring their fabrication and storage capabilities. Research is also ongoing to better understand the fundamental interaction which may stimulate thrombosis when these biomaterials are in contact with blood.

Perhaps most dramatically, in two separate laboratories, calves with a total artificial heart completely replacing the natural organ have now lived in excess of four months. These animals have demonstrated normal growth, the ability to exercise on a treadmill and, in general, to behave normally though tethered to their external energy source. Two-month survivors have now been reported in several other institutions. Animals have survived for approximately a year with implanted left ventricular assist devices. Extensive and rigorous testing of cardiac assist devices in a series of calves has validated such units for short-term investigative studies in man. Such studies have now been initiated. In addition, there has been improvement in energy converters that may be used as implantable power sources for artificial hearts. The major improvement has been seen in increased durability and reliability during bench and mock loop testing. Electrical energy converters have operated over 50 million cycles and thermal energy converters have operated for over two years without maintenance.

The important advances already attained in circulatory assistance and cardiac replacement dictate the need for further assessment of the clinical benefit of present short-term circulatory assist devices; the development and assessment of long-term, permanent assist devices; and ultimately, total cardiac replacement devices. This requires research on the physiological techniques and consequences of assisted circulation, as well as development and refinement in circulatory assist systems and components.

The potential exists to develop a long-term, permanent ventricular replacement device. However, such devices must be approached through prior experience with temporary ventricular assist devices. Near-term objectives emphasize temporary assist devices capable of providing clinically significant benefit in presumably reversible cardiac conditions. These devices will necessitate the patient being tethered to a bedside console. However, they are a required step towards the more ambitious goal of a totally implantable, long-term cardiac assist device and, ultimately, of a total cardiac replacement device.

The circulatory assistance program requires continuous careful management; periodic reassessment of intended targets in the context of technological advances and societal needs is essential.

Circulatory assistance is only one of many important applications of technology to cardiovascular research and therapy. A broad range of instrumentation and devices, both diagnostic and therapeutic, are important to and included within the nine cardiovascular program areas already cited. Examples include noninvasive methods to detect, quantify, and characterize atherosclerosis and methods to quantify infarct size, artificial heart valves, pacemakers, etc.

Program Plans

Actions. The Institute plans to:

- Continue research on the development and evaluation of implantable heart assist devices capable of taking over a significant fraction of the workload of the heart for extended periods of time
- Continue research on the development and assessment of implantable power sources and pumps suitable for permanent implantation
- Continue the clinical evaluation of temporary left ventricular assist devices directed at the short-term management of heart failure and shock
- Compare the clinical benefit and relative indications of implantable mechanical assist devices with those of much less complex assist techniques such as intraaortic counterpulsation and external, pump-mediated left heart bypass
- Continue research on the development of biocompatible materials with surface, mechanical, and transport properties suitable for specific prosthetic applications
- Continue research on and development of circulatory assist and artificial heart systems emphasizing the former and including the development of biocompatible materials, pumps, actuators, energy-conversion devices, implantable systems, devices for the transcutaneous transmission of energy, and control systems for these devices
- Continue systematic physiological evaluation of ventricular assist and cardiac replacement devices
- Maintain awareness of the societal impact of the application of circulatory assist and artificial heart devices
- Continue the US-USSR agreement on cooperation in the field of artificial heart research and development.

Schedule. Present programs involving the development of circulatory assist devices and total heart replacement devices will continue over the next five years. The near-term goals emphasize development of temporary assist devices which will provide substantial clinical benefit rather than the more ambitious goals of a totally implantable, long-term cardiac assist or replacement device. Based upon these near-term developments, permanent, fully implanted assist devices, and ultimately, cardiac replacement devices may be developed.

LUNG DISEASES

Chronic lung diseases have been increasing steadily for the past 25 years as important causes of disability and death. Chronic respiratory diseases affect an estimated 14 million Americans; emphysema, an estimated 1 million; chronic bronchitis, an estimated 7 million; and asthma, an estimated 6 million. Thus diseases of the lung constitute a major national problem of increasing dimensions. During 1974 in the United States, lung diseases accounted for an estimated 112,000 deaths, caused 130 million days lost from work, and cost the economy $18.6 billion.

In September 1972, the NHLBI appointed the Lung Diseases Panel to develop and recommend a program responsive to the legislative requirements of the National Heart, Blood Vessel, Lung, and Blood Act of 1972. The recommendations of the Lung Diseases Panel were reviewed by the Institute, the National Heart, Lung, and Blood Advisory Council, and the Interagency Technical Committee. These recommendations formed the basis for developing the Institute's expanded program in lung diseases and the plans for coordination of the overall National Program in lung diseases. The lung program and the five-year plan, as initially formulated by the Lung Diseases Panel, have been reviewed and updated annually by the Institute and the Advisory Council. In FY 76, midway through the five-year period a more extensive in-depth review and assessment was undertaken, and the recommendations resulting from this review were used to formulate the updated National Plan presented in the following sections of this report.

The Institute's program addresses immediate as well as long-range objectives and emphasizes three specific approaches of comparable importance and urgency:

- Research on the structure and function of the lung designed to gain fundamental information which will improve understanding of important factors in the promotion of health and in the prevention and treatment of lung diseases

- Expansion and development of our knowledge base for specific lung diseases which constitute national health problems and which represent areas where current information is insufficient to provide immediate solutions

- Application of available technical resources to solve specific problems in areas where immediate results in improved health can be expected.

The goals of this program have not changed, but the planned actions to implement the program have been modified to reflect new insights and advances in the field. That is, the program has responded to research findings and technological advances to capitalize on these developments.

The program goals, program status, and updated program plans are discussed in this section for each of the six program areas: structure and function of the lung, emphysema and chronic bronchitis, pediatric pulmonary diseases, fibrotic and immunologic lung diseases, respiratory failure, and pulmonary vascular diseases.

STRUCTURE AND FUNCTION OF THE LUNG

Program Background

Expansion of our present knowledge of the structure and function of the normal lung and of the modifications that result from disease is essential to any advances in diagnosis, treatment, or prevention of lung disorders. Through basic research involving molecular biology, biochemistry, immunology and cell biology, investigations of lung structure and function can contribute to understanding the causes (etiology) and processes that affect the course (pathogenesis) of lung diseases. With better insights into fundamental mechanisms, it will be possible to detect subtle structural and functional changes that characterize an early phase of a disease before clinical symptoms are manifest. These basic insights will also open new possibilities for therapeutic intervention and, in some instances, prevention of lung diseases.

Program Goals

- The primary goal of this program is to stimulate the use of fundamental disciplines such as molecular biology, biochemistry, immunology, and cell biology in studies of the structure and function of the lung in health and disease.

Program Status

It is no longer sufficient to view pulmonary function solely in terms of gas exchange. Increasingly, important aspects of pulmonary function are being traced to biochemical processes in the more than 40 types of cells that comprise the lung and reflect the diversity of its metabolic activities. Considerable progress has been made in establishing specific functions for some of these cell types, particularly the type I and type II epithelial cells of the alveoli, and the alveolar macrophage which plays a major role in lung defense mechanisms.

It is now known that the alveolar type I cell displays minimal enzymatic activity and is thus biochemically specialized to consume little oxygen. However, this metabolically inactive cell is anatomically specialized to provide a very thin barrier to diffusion of oxygen and carbon dioxide between the lung and the capillaries, thus facilitating gas exchange. On the other hand, the type II cell is metabolically active and is now believed to have an essential role in secretion of the surface-active material (surfactant) of the lung--a substance that is deficient in neonatal respiratory distress syndrome (hyaline membrane disease).*

The fact that the lungs can inactivate bradykinin (a substance which tends to lower blood pressure) and convert angiotensin I to angiotensin II (one of the most potent hypertensive substances known) suggests a role of the lungs in blood pressure homeostasis. Another important finding is that one of the

*See *Pediatric Pulmonary Diseases*, pp. 87-88.

enzymes responsible for this metabolic change (i.e., the pulmonary angiotensin converting enzyme) is located on the membrane of a specific lung cell type, the endothelial cell, correlating the ultrastructure of the lungs with a specific metabolic activity. The finding that a single enzyme can both degrade bradykinin and convert angiotensin I to angiotensin II suggests that the pulmonary control of systemic blood pressure can now be investigated at the molecular level. Furthermore, the technology now exists for visualizing pulmonary converting enzyme in situ on the membranes of the lung endothelial cell. Therefore, it is now opportune to examine the effect of disease processes on the ability of the lungs to metabolize circulating hormones.

Excessive secretion of mucus or secretion of abnormal mucus is associated with many pulmonary diseases. However, in the normal individual, mucus secretion is an important defense mechanism against inhaled particles and toxic substances. Such particles are removed by the regular motion of the fine hairlike projections, or cilia, of the cells lining the airways of the lung. Because of the relatively small amounts of mucus found in normal individuals, collection of normal tracheal mucus has been difficult, but progress has been made in experimental animals. Moreover, techniques for measuring mucociliary clearance have been developed in animals to the point that they can now be applied to man and are being used to evaluate how environmental factors and respiratory disease affect this function. An area for future investigation is the chemistry of normal respiratory tract mucus.

In studies of the structural components of the lung (collagen, elastin, proteoglycans and basement membrane), considerable progress has been made in elucidating the structure of two: collagen and elastin. It is important to extend such investigations to proteoglycans and basement membrane. Because collagen proliferation occurs in fibrotic diseases and elastin destruction is characteristic of the late stages of emphysema, current studies on the synthesis and degradation of these substances must be continued and expanded.*

While the emphasis of this segment of the National Plan is to increase our knowledge of cellular and molecular biology of lung tissues, some notable progress has been made in the application of new knowledge about lung physiology to a better understanding of respiratory disease. New tests of gas flow, gas exchange, tissue elasticity, and surface tension are being applied to special population groups in an attempt to identify individuals who may be at risk of developing lung disease and to evaluate the effects of intervention to prevent progression of such disease if it is already present. In recent years significant progress has also been made in understanding how the elastic surface properties of lung tissue effect gas exchange. This new knowledge has enabled the development of better methods for artificial ventilation and inhalation therapy, which have markedly reduced mortality caused by acute respiratory insufficiency from pneumonia, respiratory distress syndrome of the infant and adult, emphysema, and chronic bronchitis.

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*See under *Fibrotic and Immunologic Lung Diseases*, pp. 90-91.

Program Plans

Actions. The Institute plans to:

- Expand studies on nonrespiratory functions of the lung by continuing targeted studies on individual lung cell populations in defined environments; by expanding the program in basic lung cell biology, emphasizing such areas as the correlation of ultrastructural and metabolic studies; and by fostering the interdisciplinary approach to studies of alveolar macrophages, characterization of lung connective tissue components, the structure, synthesis, and physiochemical properties of bronchial mucus, and the integration of physiological studies with structural investigations of the lung.

- Hold workshops designed to attract basic scientists not previously involved with lung research by instituting pulmonary seminars at national meetings to acquaint basic scientists (especially biochemists, physical chemists, immunologists and cell biologists) with the challenges in the field of pulmonary research, by emphasizing investigator-initiated research grants on the structure and function of the lung, and by continuing to encourage multidisciplinary programs that facilitate working relationships between clinical and fundamental researchers.

Schedule. New programs on isolation, characterization, and metabolism of lung proteoglycans will be initiated in FY 77. Two workshops, one on the metabolism of the alveolar macrophages and one on basement membranes, will be sponsored; and a three-day course on lung cell separation, identification, and culture will be held. Additional research projects on structure and function of the lung will be encouraged through investigator-initiated research grants in all areas discussed above. Active research on the structure and function of the lung will continue to be fostered by the Institute over the next five years.

EMPHYSEMA AND CHRONIC BRONCHITIS

Program Background

The study of emphysema and chronic bronchitis is the primary focus of this program, although asthma and bronchiectasis and other similar obstructive disorders contribute to the the national health problems of chronic obstructive lung disease (COLD). All diseases within the COLD classification are characterized by chronic or recurrent obstruction to airflow within the lung, breathlessness, cough, and susceptibility to respiratory failure. These diseases are associated with high morbidity and, in late stages, with mortality. In 1974, 41,000 died in the United States from these diseases: this represents the sixth highest mortality rate in the nation.

Since 1968, there has been a growing tendency by preparers of death certificates to include a variety of specific diseases such as emphysema and chronic

bronchitis under the more general classifications of chronic obstructive airway, pulmonary, or respiratory disease. For statistical purposes at the National Center for Health Statistics (NCHS), nonspecific classifications have been grouped under a single heading officially referred to as Chronic Obstructive Lung Disease (COLD). As shown in Figure 7, the death rate from bronchitis, emphysema, and asthma increased steadily from 1955 to 1968 but appeared to decline from 1969 through 1974. However, when the death rates from the post-1968 nonspecific classifications (COLD) are added to the death rates recorded specifically due to bronchitis, emphysema, and asthma, the trend of the total COLD death rate approximates the pre-1968 trend which is essentially parallel to that of lung cancer. Thus, the previously reported reduction in death rate from emphysema and chronic bronchitis appears to be in error. However, the rates of increase for these specific pulmonary diseases cannot be determined accurately from the existing data.

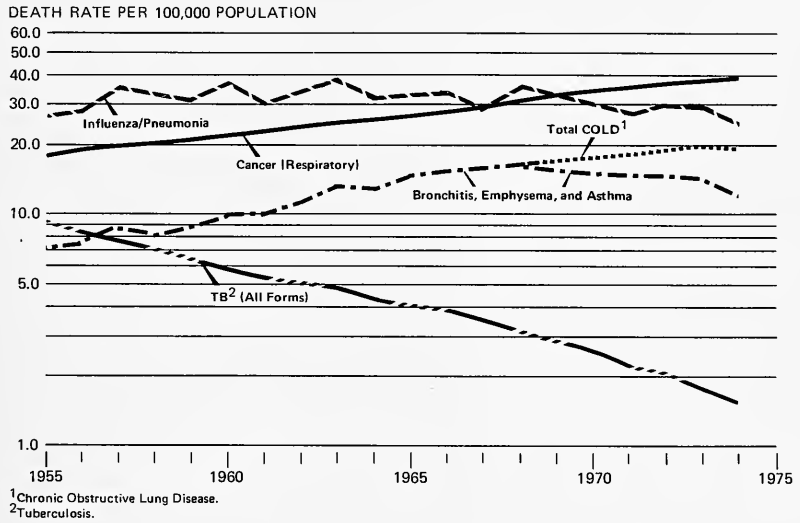

Figure 7. **DEATH RATES FROM INFLUENZA/PNEUMONIA, CHRONIC OBSTRUCTIVE LUNG DISEASE, TUBERCULOSIS, AND RESPIRATORY CANCER, 1955-74**

Because emphysema and chronic bronchitis are usually not detected before clinical symptoms appear, they are presently irreversible by the time they are diagnosed. The prevention and effective treatment of these disorders depend on an understanding of the factors that predispose to or exacerbate them and on the

development of tests to identify structural and functional abnormalities before the disease reaches the irreversible stage. Both host and environmental factors contribute to development of these diseases; consequently, it is important to be able to identify individuals who are at risk of developing lung disease because of a genetically determined predisposition, or whose environment or life style (especially cigarette smoking) places them at risk. Basic research involving biochemistry, immunology, genetics, cell biology, and physiology is essential to develop an understanding of how etiologic agents produce their effects and how the pathogenesis of the disease can be modified or arrested. For individuals genetically at risk of developing COLD, environmental factors exacerbating this risk become even more serious.

Program Goals

Major goals of this program are to:

- Prevent chronic emphysema and bronchitis by identifying and controlling risk factors, and to arrest disease development by detecting structural and functional abnormalities early enough for therapeutic intervention
- Improve treatment and rehabilitative regimens for established and progressive chronic obstructive lung disease
- Draw upon basic disciplines to elucidate the causes and pathogenetic mechanisms that result in chronic emphysema and bronchitis.

Program Status

Sophisticated tests are now available to detect subtle alterations in pulmonary function that may be early indicators of progressive chronic obstructive lung disease. Progress has been made in using these tests to compare their effectiveness in detecting early changes in lung function in individuals and in population groups exposed to various risk factors. Findings from these studies indicate that socioeconomic status, airways reactivity, and allergies are risk factors in addition to the already well-known factors such as smoking, genetic predisposition, and exposure to various airborne substances. Moreover, risk may be increased by the interaction of such factors as socioeconomic status, genetic predisposition, and cigarette smoking. These suggestive observations require further exploration in future studies.

In a population study to determine whether abnormalities of pulmonary function in smokers will be arrested or reversed after smoking cessation, it has been shown that the abnormalities, once present, are progressive and that age as well as smoking contributes to the downhill course. However, the rate at which deterioration occurs in an individual appears to be a more sensitive measure of severity than is the absolute magnitude of the pulmonary abnormality. These significant new findings warrant further study in individuals and population groups. It is especially important to learn whether the earliest detectable evidence of airway obstruction will be reversed if an individual stops smoking and to establish whether mild, reversible airway dysfunction is a forerunner of more severe, irreversible obstructive disease.

It is well established that a genetic defect resulting in a deficiency of the enzyme alpha-1-antitrypsin is a factor in the development of a severe form of familial emphysema which attacks young adults. There is evidence that in such individuals an abnormal alpha-1-antitrypsin molecule is produced in the liver, but it is not secreted into the blood stream and thus fails to reach the lungs. Studies are in progress to elucidate this abnormality with respect to alpha-1-antitrypsin secretion and its interaction with, and inactivation of, proteolytic enzymes normally found in the lung. A recent study indicates that the trace metal cadmium can inactivate alpha-1-antitrypsin when mixed with serum at concentrations comparable to those found in the blood stream of cadmium workers. This is a significant finding in that industrial exposure to cadmium is often associated with development of severe centrilobular emphysema. Thus, defective alpha-1-antitrypsin may contribute to a broader spectrum of cases than familial emphysema alone.

Genetic and biochemical studies of familial emphysema suggest the possibility of alpha-1-antitrypsin replacement therapy. Synthetic peptides which have functional effects similar to those of alpha-1-antitrypsin (i.e., they inhibit or prevent degradation of lung tissue elastin) are now available and have been distributed to scientists who are engaged in studies of inhibitory mechanisms. Studies of lung structure and function have contributed to our understanding of the etiology and pathogenesis of chronic bronchitis and emphysema. Since it has been shown that proteolysis of lung tissue elastin, rather than collagen, is involved in the development of emphysema, it is important to study elastase for its ability to produce emphysema-like changes in animal lungs after instillation into the airways. Immunohistochemical techniques should be used in conjunction with standard microscopic studies to trace the tissue distribution of the pure leukocyte elastase in the lungs of experimental animals. Similar techniques should be used in an effort to detect leukocyte elastase in cells and tissues from diseased human lungs.

Significant advances have been made in methodologies for measuring the velocity of mucus transport by the ciliated epithelium of the airways, in collecting normal mucus for physicochemical analysis, and in measuring transtracheal water and ion fluxes. These advances should provide new approaches to study the role of the pulmonary secretions in chronic obstructive lung diseases. Furthermore, animal and tissue culture models of pulmonary infections are being established which should prove valuable in studying the role of airway infection in the pathogenesis of chronic bronchitis.

The roles of interaction of proteases, antiproteases, and cigarette smoking in the pathogenesis and etiology of chronic obstructive lung disease as well as allergic, immunologic, and pharmacologic factors need to be investigated. The role of the autonomic nervous system and related neural control mechanisms in these diseases and the role of abnormal bronchial secretions or ciliary activity require exploration. The suggestion that abnormal bronchial reactivity may have a role in the pathogenesis of chronic bronchitis requires further study.

The irreversibility of late chronic obstructive lung disease limits the success that can be achieved in the area of treatment. Although a large number of therapies are recommended, they are costly and of uncertain efficacy. Such measures as long-term oxygen therapy, assisted ventilation, bronchodilators, corticosteroids, antimicrobials, mucolytics, chest physiotherapy, rehabilitation, and intermittent positive-pressure breathing are being critically assessed.

Furthermore, innovative approaches for new therapeutic techniques based on information related to the etiology and pathogenesis of the disease process will be developed. In addition, fundamental studies in neuromuscular physiology might provide therapeutic approaches to breathing training and respiratory muscle reeducation procedures, as well as more direct approaches to the relief of the sensation of breathlessness. Nevertheless, it is anticipated that the most effective therapeutic approaches will be those which are applied to patients with relatively early disease.

Program Plans

Actions. The Institute plans to:

- Expand studies of early detection by continuing physiologic studies to define the specificity and sensitivity of simple pulmonary function tests to detect early signs of obstructive lung disease and by encouraging studies to demonstrate that individuals with early dysfunction of the airways are at high risk for development of irreversible, symptomatic, chronic obstructive lung disease

- Extend investigations to assess the value and role of commonly used treatment modalities for established chronic lung disease, including intermittent positive-pressure breathing, bronchodilators, antimicrobials, corticosteroids, and chest physiotherapy as well as psychological support to patients and families

- Continue studies of neuromuscular ventilatory control mechanisms in relation to possible therapeutic procedures such as bilateral removal of the carotid chemoreceptor bodies

- Extend investigations to elucidate the roles of host factors and environmental agents in the etiology and pathogenesis of emphysema and chronic bronchitis by continuing interdisciplinary programs in Specialized Centers of Research, maintaining targeted programs using selected populations, and by encouraging investigator-initiated studies.

Schedule. Studies assessing the prevalence of chronic obstructive lung disease in several defined populations will be completed by FY 78. Programs investigating alpha-1-antitrypsin will be completed by FY 77, while the research into smoking and chronic airway obstruction will continue through FY 78. Information gained from these extensive epidemiologic programs will be used to develop new activities in the areas of early diagnosis and identification of individuals at risk. One such study, an assessment of pulmonary function in individuals heterozygous for alpha-1-antitrypsin deficiency, will begin in FY 77. Biochemical characterization of alpha-1-antitrypsin and evaluation of the role of neutral proteases in the pathophysiology of chronic obstructive lung diseases will continue to be major aspects of this program area through FY 79. Suggested standardized procedures for the assay of human leukocyte elastase will be offered during FY 77 to assist in the comparison of data among laboratories.

A workshop to evaluate the efficacy of bilateral carotid body resection in the management of severe obstructive lung disease will be conducted during FY 77.

PEDIATRIC PULMONARY DISEASES

Program Background

Neonatal respiratory distress syndrome (NRDS) or hyaline membrane disease, cystic fibrosis, and bronchiolitis are diseases of infancy or childhood that involve the lung and constitute major health problems in this age group. About 40,000 babies are born each year with NRDS and many of these will die unless given prompt treatment. In the past, NRDS was one of the most frequent causes of death in the newborn infant, but it can be treated successfully if recognized early enough and treated promptly with the sophisticated techniques now available. Since this is a disease of prematurity, it is especially important that it be diagnosed prenatally so that preparation can be made for suitable treatment of newborns who are at risk. Recently developed techniques for analysis of amniotic fluid have made possible such early diagnosis.

Cystic fibrosis is a genetically determined disease that affects many organs, but the pulmonary complications of this disease are major sources of morbidity and mortality. The disease occurs in one of every 2,000 live births, and approximately 5 percent of the general population in the United States carries the gene for this disorder. Characterized by an excessive secretion of possibly abnormal mucus, cystic fibrosis was formerly fatal in early childhood. However, with advances in therapeutic techniques, children severely handicapped by this disorder sometimes now live into adolesence and beyond.

Bronchiolitis, a common infectious disease of childhood, is of interest because it is believed that it may contribute to development of chronic lung disease in later life.

Program Goals

The major program goals are to:

- Develop improved methods for early diagnosis of neonatal respiratory distress syndrome (hyaline membrane disease) and design more effective modes of therapy. Until methods to prevent this disease are available, early diagnosis and prompt initiation of therapy are essential.

- Assess present modes of therapy for cystic fibrosis and develop new methods based on a better understanding of the basic pathology of mucus production and secretion in this disease.

- Foster long-term studies of the effects of bronchiolitis in childhood on the risk of developing chronic lung disease in the adult.

Program Status

Amniocentesis, the removal of amniotic fluid during fetal development, has advanced to the point that it is now a safe and widely used procedure. Coupled with advances in identifying surface active material of the lung and its precursors, amniocentesis permits effective early diagnosis of lung immaturity, which is a risk factor for development of NRDS. The use of constant positive airway pressure (CPAP) has also become an acceptable and widely used procedure to treat NRDS and is meeting with noteworthy success. This procedure maintains a pressure above atmospheric at the airway opening throughout the respiratory cycle during spontaneous breathing, thus ensuring an adequate oxygen supply to the infant with immature lungs.

NRDS is thought to be caused by immaturity of the lungs, and its incidence can be correlated with the degree of prematurity and by a low birth weight if this is the result of premature delivery of the infant. Since glucocorticoids increase the maturity of lung tissue in fetal animals, administration of these drugs to human mothers is being investigated. A recently initiated, randomized, double-blind, controlled trial will evaluate the effectiveness of corticosteroids administered 24 to 74 hours before birth in decreasing the incidence of NRDS. The trial will also attempt to determine whether such therapy has any adverse short-term or long-term (up to 18 months) effects on the infant.

Although these advances are reflected in a marked reduction of infant mortality, the important challenge for the future is to prevent NRDS, a challenge being addressed through fundamental investigations of lung development and the factors that delay maturity.

Since cystic fibrosis is a genetically determined disease, there is great interest in identifying underlying biochemical changes that can be the basis of early detection. One such factor--the ciliary inhibitory factor, which is detected by its effect on ciliary action--continues to be studied. Progress has been made in isolating and characterizing the molecule that produces this effect on cilia. It has been obtained in culture from the cells of parents of cystic fibrosis patients, although the parents are heterozygous for the genetic determinants of the disease. These studies must be expanded and continued. In addition, further research is needed to elucidate the characteristics of the possibly abnormal mucus in cystic fibrosis patients and the factors that cause the abnormality.

Before long-term follow-up studies of pulmonary function in infants and young children with bronchiolitis lung diseases can be effectively undertaken, suitable methods to measure pulmonary function in this age group are essential. Some progress has been made in measuring pulmonary compliance in the infant, but the development of a battery of tests for assessing pulmonary function in the very young child is still a challenge to be met.

Program Plans

Actions. The Institute plans to:

- Expand interdisciplinary basic studies of changes associated with neonatal respiratory distress syndrome and cystic fibrosis by encouraging investigator-initiated research on biochemical and physiologic features of the prenatal and neonatal environment that predispose to NRDS and on the biochemical and biophysical alterations of mucus and basic cellular function in cystic fibrosis, and by extending interdisciplinary studies in the Specialized Centers of Research

- Continue targeted programs to develop techniques and devices to assess pulmonary function in infants and young children, and to utilize these in longitudinal studies to assess the long-term natural history of pulmonary diseases in childhood

- Initiate controlled clinical trials to evaluate the efficacy of widely used but inadequately assessed approaches and devices for the treatment of cystic fibrosis, bronchiolitis, and childhood asthma--especially physical therapy, bronchodilators, and pharmacologic agents.

Schedule. While program development in the area of neonatal respiratory distress will be kept at a steady level through FY 79, programs will expand in the area of bronchiolitis and cystic fibrosis. A workshop on bronchiolitis is scheduled to provide the intial impetus for expanding research in this area. Programs dealing with the pathogenesis of bronchiolitis and cystic fibrosis will continue to increase through FY 79. Moderate increments are anticipated through FY 81 with increasing emphasis on the natural history of these disorders.

FIBROTIC AND IMMUNOLOGIC LUNG DISEASES

Program Background

The fibrotic and immunologic diseases addressed in this program encompass a variety of disorders--interstitial, alveolar filling, or obstructive--that result from the interaction of various host and environmental factors. In most of these diseases, immunologic factors play a prominent role in pathogenesis, and many of these disorders can be alleviated and sometimes prevented if the offending substances are removed or their effects suppressed. Specific disorders included in this program are asthma, an allergic obstructive disease; hypersensitivity pneumonitis (e.g., farmer's lung), an allergic fibrotic disease; a number of occupational diseases (e.g., asbestosis and silicosis) due to environmental exposures to inorganic dusts; and sarcoidosis, a prevalent granulomatous disease of unknown etiology. Because most of these diseases can be prevented, a major emphasis of the program is identification of offending agents. However, as exposure often is unavoidable, an equally important emphasis is elucidation of the mechanisms by which environmental and host factors interact to produce disease, and how these reactions can be modified or prevented.

Program Goals

- The primary goal of this program is to foster fundamental research to determine the host and environmental factors that are implicated in fibrotic and immunologic diseases of the lung, and to elucidate the mechanisms by which these factors cause pathogenetic changes.

Program Status

In many asthmatics, acute episodes are precipitated by exposure to antigens. Recent research has defined many relationships between immunologic reactions and the release of chemical mediators (histamine, bradykinin, and some prostaglandins) directly responsible for the functional abnormalities. The mechanism of immunoglobulin E, which acts as a "gatekeeper" to facilitate filtering and deposition of immune complexes that induce allergic reactions in pulmonary tissue, has also been elucidated. These findings are relevant to a number of fibrotic and immunologic lung diseases, and they need to be studied in relation to specific disorders.

Progress in the study of sarcoidosis has been impeded by the absence of either a reliable in vitro test or a suitable animal model. It has been suggested that the disease process involves both endogenous and exogenous agents and exposure of genetically susceptible individuals to the causative environmental agents. This may be of particular importance in view of recent findings that there may be an association between two specific antigens (HLA antigens) with sarcoidosis. Although the data are still preliminary, it has been shown that sarcoidosis is four times more frequent in individuals who carry these antigens than in those who lack them. This important observation could provide a genetic marker or markers to identify a high-risk status.

Recent advances in studies of farmer's lung and related disorders have shown that hypersensitivity pneumonitis is more prevalent than had been realized in the past and that abatement will occur if the patient is no longer exposed to the offending agent (antigen) in molds, yeast, and organic dusts. A challenge to be met is the identification of possible sources of such antigens in home and working environments, as it is now clear that common equipment, such as airconditioners, may harbor molds.

Some progress has been made in developing animal models of hypersensitivity pneumonitis by using antigens of plant origin (phytomitogens). This is an essential step for future studies using animal models for investigations that cannot appropriately be done in patients.

Studies in progress which will receive further attention in the future show that interstitial fibrotic lung diseases are associated with what appears to be an excess of connective tissue. Nevertheless, studies of material obtained from human lung biopsies indicate that the average density of lung collagen, the rates of collagen synthesis per cell, and the percentage of collagen synthesis are normal. These findings suggest that collagen abnormalities might be related to local changes in lung structure which result in severe physiological abnormalities but which do not affect the average collagen density in the lung. Clarification of the role of collagen in fibrotic lung diseases may

result from ongoing studies of cell types that are responsible for collagen synthesis and studies of how the synthetic processes are affected by injury due to environmental agents.

Program Plans

Actions. The Institute plans to:

- Continue to foster investigations relative to immunologic responses and other defense mechanisms of the lung involved in the development of fibrotic and immunologic lung diseases by encouraging development of investigator-initiated program projects involving both basic and clinical disciplines, by initiating targeted programs to develop pharmacological agents that will modify connective tissue reactions associated with fibrotic disease, and by initiating targeted programs to investigate etiologic factors in high-risk population groups.

- Continue to emphasize the development of animal models of fibrotic and immunologic lung diseases by encouraging investigator-initiated studies.

- Encourage studies of the effects of inorganic and organic dusts on the development of pulmonary granulomatous and fibrotic lesions. Projects concerned with the in vitro immunologic response of bronchoalveolar T and B lymphocytes and macrophages to these dusts (e.g., asbestos fibers, beryllium salts, silica particles) will be emphasized.

- Foster the use of in vitro tests for granulomatous diseases to define populations at risk and to study the natural history and sequelae of these diseases.

Schedule. Investigative pursuits relative to immunologic and allergic mechanisms involved in the development of fibrotic, granulomatous, and airway pulmonary diseases will be initiated during the period FY 77 through FY 81. A workshop on the reaction of host defense mechanisms in infectious pneumonitis is planned for FY 77. Epidemiologic studies of hypersensitivity pneumonitis and fibrotic lung disease emphasizing their pathogenesis and natural history will continue through FY 79. All of the action areas represent incrementally increasing activity between FY 77 and FY 81.

RESPIRATORY FAILURE

Program Background

Respiratory failure occurs when alveolar ventilation is insufficient to provide adequate gas exchange. It occurs as a consequence of many types of pulmonary, nonpulmonary, acute, and chronic disorders and is among the most common causes of death from postoperative and other major traumas. It also occurs in late stages of such chronic disorders as emphysema and chronic bronchitis. Nevertheless, respiratory failure can be successfully treated

if it is recognized early and therapy is instituted promptly. Thus, major research efforts in this program are to identify predisposing factors so that respiratory failure can be detected early, and to develop modes of therapy that will be effective even in advanced stages of this disorder.

Program Goals

The major goals of this program are to:

- Improve early detection of respiratory failure by elucidating pathogenetic mechanisms and by developing more precise diagnostic techniques

- Improve management and therapy by critically assessing modes of therapy currently in use for respiratory failure, by developing devices for continuous monitoring of changes during therapy, and by developing devices for more effective treatment of acute respiratory distress syndrome.

Program Status

Major research emphasis in respiratory failure has been on therapeutic approaches to life support in the critically ill patient and on mprovement of gas exchange. However, mechanisms causing severe lung injury, which occurs in respiratory failure and its subsequent repair, remain an important and largely unexplored area. Studies are now under way to determine whether enzymes such as elastase, trypsin, and papain have a role in the pathogenesis of diffuse lung injury. A more precise awareness of the biochemical and physiological responses of the lung to the various types of injury that lead to respiratory failure syndrome will aid in its early diagnosis as well as provide the rationale for specific types of intervention.

Although there has been noteworthy progress in the development of devices to treat respiratory failure, as yet, none of these has passed the critical test of a controlled clinical trial. Development of extracorporeal membrane oxygenators (an artificial lung that oxygenates blood outside of the body when lung function is so impaired that gas exchange is inadequate) has progressed to the point that these devices are now being tested as adjuncts to conventional modes of therapy for acutely ill patients with adult respiratory distress syndrome. Because of the large number of patients that must be studied in such a clinical trial, the results will not be known for at least another year.

Considerable technological progress has been made to allow continuous and rapid monitoring of cardiopulmonary function, permitting an assessment of response to treatment. For example, indwelling monitors to assess arterial blood gas tensions are in various stages of development, although none are yet in common use. However, noninvasive sensors to measure oxygen tension on a continuous basis will soon be commercially available and will have a valuable role in monitoring patients under treatment for acute respiratory distress syndrome.

Because respiratory failure is reversible if identified early enough for prompt treatment, the development of sensitive, rapid, and reliable methods for early detection is of paramount importance.

Program Plans

Actions. The Institute plans to:

- Initiate research programs addressed to the mechanisms of lung tissue injury, cellular response, and subsequent repair associated with respiratory failure by encouraging investigator-initiated studies, and by continuing collection of clinical data that will better define the natural history of the syndrome

- Expand programs to improve the management and treatment of patients in respiratory failure by expanding programs of technological development and evaluation of techniques capable of early detection (i.e., continuous blood gas sensor devices, ventilation-perfusion measurements, and lung-water flux techniques), by initiating targeted programs to include the testing and evaluation of devices to monitor other measurements of pulmonary function, and by continuing targeted programs for the assessment of promising modes of respiratory support.

Schedule. During FY 77, programs for the development and evaluation of techniques for early detection, improved respiratory support, and clinical data collection will continue. A workshop on the basic mechanisms of lung response to acute injury will be held to consolidate the data available on the etiology and pathogenesis of the damage and repair processes. This workshop will be followed by a targeted research program aimed at a better understanding of these mechanisms. This, in turn, could lead to improved management and treatment of respiratory failure. Further program developments of techniques to identify and quantitate the early development of this syndrome will also be pursued. These programs will continue to increase gradually through FY 81. Their emphasis will be on understanding and treating the pathogenesis and pathology of respiratory failure.

PULMONARY VASCULAR DISEASES

Program Background

Pulmonary vascular diseases, including pulmonary hypertension, pulmonary edema, and cor pulmonale are serious lung disorders with often devastating consequences. However, precise data on their contributions to morbidity and mortality, or on their incidence and prevalence are not available owing to lack of dependable methods for early and precise diagnosis. Furthermore, when pulmonary circulatory involvement is recognized, it is often at a late stage in the evolution of the disorder so that treatment is ineffective. These diseases could be treated if they could be identified reliably and early in their course. Development of noninvasive techniques that could be used

repeatedly without undue discomfort to the patient would permit study of the course of these disorders and the long-term benefits of therapy. Fundamental investigations into the causes and pathogenesis of these disorders are essential.

Program Goals

The three program goals are to:

- Stimulate developmemt of reliable noninvasive techniques for assessing the ventricular hypertrophy associated with cor pulmonale, and for diagnosing pulmonary hypertension without the need for cardiac catheterization
- Encourage development of animal models of cor pulmonale and pulmonary hypertension to be used in the investigation of pathogenic mechanisms of these diseases
- Foster multidisciplinary studies aimed at understanding the dynamics of fluid, electrolyte, and protein exchange in pulmonary edema.

Program Status

Alterations in the pulmonary vasculature are controlled by the sympathetic and parasympathetic nervous systems which mediate their effects through secretions (neurohumors) that cause contraction or dilation of the blood vessels. Progress has been made in determining how these chemical mediators control the pulmonary circulation in health and modify it in disease. In recent years, many other compounds (catecholamines, peptides, hormones, prostaglandins) that have lung vasomotor effects have been identified. Some of the complex mechanisms involved in the transformation and action of these substances have been clarified. In some instances, the cellular and subcellular sites of these changes have been established. For example, the pulmonary capillary endothelial surface of the lung has been identified as the major site for transformation of angiotensin I into angiotensin II (a potent vasopressor). Nevertheless, further fundamental research and suitable animal models are needed to relate such chemical transformations to the changes in the pulmonary vasculature that occur in pulmonary vascular diseases.

Progress has been made in applying available technologies to develop noninvasive methods to assess pulmonary hypertension. These methods must still be evaluated. Techniques have also been developed to measure abnormal lung-water flux using insoluble gases and may soon be ready to apply to the detection of pulmonary edema in patients.

Screening tests of pulmonary function, including exercise testing, have revealed that some cases of unexplained breathing difficulty (dyspnea) are due to pulmonary vascular obstruction. Also, systematic examination of the lungs from infants believed to have succumbed to "sudden infant death syndrome" show abnormalties in pulmonary circulation. These findings suggest that pulmonary vascular alterations may be an important clue to other disorders.

Effective therapy for pulmonary hypertension, cor pulmonale, and pulmonary edema remains a major challenge. The role of oxygen therapy in treating a variety of lung diseases has been established, and it is now being used in a wider spectrum of patients. Nevertheless, the basic challenges with regard to pulmonary vascular diseases are to have a better understanding of the pharmacologic agents that alter the pulmonary circulation and then to determine their usefulness as therapeutic agents.

Studies of the natural history of the pulmonary vascular diseases must await the further development of reliable, sensitive tests that can be used to identify subtle changes early in the course of these disorders and that can be used repeatedly even on very ill patients.

Program Plans

Actions. The Institute plans to:

- Encourage fundamental investigations of the normal and abnormal pulmonary circulation. Particular attention will be paid to the relationship between blood flow and surface area; to the metabolism of vasoactive substances in health, exercise, and disease; and to the assessment of the ability of the lungs to transform drugs, hormones, and other substances.

- Foster fundamental studies of the dynamics of lung-water flux in order to understand factors contributing to abnormal water balance.

- Improve diagnosis of pulmonary vascular diseases by developing technology for detecting pulmonary abnormalities in patients in their home or working environments.

- Improve therapy by evaluating the utility of currently available pharmacological agents in reducing elevated pulmonary artery pressure, and by expanding studies of the role of oxygen therapy in patients with chronic obstructive lung disease (before the onset of cor pulmonale) and in other appropriate candidates for such treatment.

Schedule. Basic research on normal and abnormal behavior of the pulmonary circulation and fundamental studies of lung-water flux will be continued through investigator-initiated research grants. Programs designed to assess the prevention and incidence of pulmonary hypertension and to evaluate the therapeutic usefulness of currently available pharmacologic agents to alter elevated pulmonary artery pressure and its sequelae will begin in FY 78. Programs to evaluate the role of oxygen therapy for treatment of chronic lung disease and pulmonary hypertension entered the planning stage in FY 76; actual clinical trials will begin in FY 77, with interim results available in FY 78. Programs to pursue the development of laboratory tests for the accurate diagnosis of pulmonary embolism and to evaluate diagnostic techniques will contribute to increasing program activity from FY 78 to FY 81.

BLOOD DISEASES AND BLOOD RESOURCES

With the enactment of Public Law 94-278 in 1976, the National Heart and Lung Institute (NHLI) became the National Heart, Lung, and Blood Institute (NHLBI). Although blood research has long constituted an integral part of the Institute's program, this name change signaled the federal government's recognition of the importance of a field formerly unrepresented on the roster of categorical institutes at the National Institutes of Health (NIH). It does not mean, however, that all research pertaining to blood will become the exclusive province of the NHLBI.

Research approaches to blood currently encompass an enormous range of problems involving the formed elements (red blood cells, leukocytes or white blood cells, and platelets) and the whole complex of plasma proteins essential for control of the clotting mechanisms and many other functions. The time has long since passed when hematology was a single discipline concerned mainly with blood cells. Today, the study of the blood groups, the numerous genetic variances of hemoglobins and red cell enzymes, the hemostatic mechanism, and the many applications of the science of blood banking have become subspecialties in their own right.

A discipline which crosses so many boundaries needs special attention. The mandate now given to the Institute calls for the coordination of blood research throughout the NIH and other federal agencies in addition to the development of a strong program within the NHLBI. The NHLBI has become the focal point for research in blood diseases and in the science of blood banking and related logistics. Blood is at once the object of research into its role in health and disease and a resource involving donors, recipients, blood bankers, scientists, and administrators, and the tasks of the NHLBI embrace all of these aspects.

This section of the Fourth Report of the Director of the NHLBI updates the Institute's programs in blood diseases and resources presented in previous reports of the Director. It deals with four major areas of blood diseases and blood resources: bleeding and clotting disorders, sickle cell disease, disorders of the red blood cell, and blood resources.

The Institute sponsors a comprehensive program in these four areas including fundamental and clinical research, professional development and training; and prevention, education, and control activities. The aim at all times is the rapid, but orderly, application of new knowledge to health care. To maximize scarce resources, both financial and human, the Institute actively coordinates its efforts with both federal and nonfederal programs involving blood. This year's report continues to review the Institute's program goals, progress, actions, and schedules.

BLEEDING AND CLOTTING DISORDERS

Normal hemostasis (blood clotting) involves an extremely complex system consisting of protein coagulant factors and cellular platelets that must stop

leaks from within the vascular system and simultaneously maintain fluidity within that system. The platelets adhere to the edges of a severed vessel and rapidly form a hemostatic plug. The protein coagulant factors ultimately form the insoluble fibrin to make a definitive repair. Understanding of this system and its control mechanisms has grown dramatically within the past decade.

As is the case with many sophisticated systems in nature, the hemostatic process may be disrupted for various reasons and at various points. Depending upon the nature of the defect, excessive bleeding (a hemorrhagic state) or an abnormal tendency to clot (a thrombotic state) may result. Although inherited problems of coagulation are relatively uncommon, an individual so afflicted may suffer from a life-long bleeding disorder which places substantial demands on the medical care system. In addition, acquired blood coagulation disorders may be secondarily associated with many common diseases and procedures, often presenting physicians with difficult problems in detection, diagnosis, and therapy.

When the hemostatic defect results in a thrombotic disorder, many of which are acquired, morbidity will depend upon the organ in which the blood supply has been deranged because of the resulting vascular occlusion. For example, thrombosis in a leg vein will result in a disrupted blood flow within the limb and may also pose the danger of pulmonary embolus. The thrombotic process is believed to contribute to the initiation and propagation of arterial occlusive disease with damage to heart, brain, extremities, and other organs depending upon the location of the occluded artery.

ARTERIAL THROMBOSIS

Program Background

Arterial occlusive disease presents an interdisciplinary problem. The clinical sequelae of this disease process include some of the major causes of death and disability in the United States: stroke, myocardial infarction, and peripheral vascular disease.

Program Goals

- Improved diagnosis and therapy of these disorders and their ultimate prevention are the aims of the complex of laboratory and clinical investigations which constitute this program.

Program Status

The interaction of the hemostatic system and the blood vessel wall has become more evident not only in the production of the final thrombotic lesion but also in the initiation of the arteriosclerotic process. The tendency of vascular cells to proliferate into thickened vessel linings has been shown to be governed, in part, by factors carried within the platelets.

Platelets have a role in keeping the vessel wall intact, and they form a major component of the arterial thrombotic lesion. Platelets interact with the blood

vessel wall during several phases of the atherosclerotic process.* Immediately after initial injury, they appear to serve as a transient lining. During the healing process, they appear to stimulate blood vessel cell growth, and platelets are also involved in the final thrombotic episode.

The various forms of vascular connective tissues have now been characterized. Each tissue has a different clotting activity varying from vessel to vessel and with age. Measurement of platelet survival and turnover has increased our understanding of the role of these cells in arterial disease. In von Willebrand's disease** platelet activity is subnormal. Pigs with this disease, unlike normal pigs, appear not to develop atherosclerosis. Blood vessel cells in tissue culture can now be made to synthesize various macromolecules; for example, endothelial cells synthesize a component of factor VIII, one of the major blood clotting factors.

In the treatment of arterial thrombotic disorders, emphasis has shifted from inhibitors of blood coagulation to inhibitors of platelet function. Clinical trials have been performed which suggest the efficacy of prophylactic treatment of cerebral or coronary occlusive disease with agents such as aspirin which inhibit certain platelet responses.

An interdisciplinary research approach is needed to solve complex thrombotic problems. Past experience has shown that the combination of resources and basic and clinical research results in a meaningful attack on such problems. Accordingly, the Institute is supporting three Specialized Centers of Research (SCORs) in Thrombosis*** to focus resources, facilities, and manpower to improve the diagnosis, treatment, and prevention of these disorders.

Program Plans

Actions. The Institute plans to:

- Encourage studies of platelet biology, including biochemistry of the platelet surface, participation of plasma protein in platelet-vessel interaction, characteristics of the platelet membrane that make the platelet unique, and further development of platelet labeling methods and their use in identifying blood vessel injury and thrombus formation.

- Continue studies of blood vessel wall biology, including cell proliferation, tissue culture, and translation of tissue culture results to animal and clinical models. Studies on the basis of selective cell stimulation or growth suppression and on the existence of identifiable chemical mechanisms will be encouraged.

- Encourage development of animal models with bleeding defects suitable for atherogenic studies. Through such models the

*See under *Arteriosclerosis*, p. 47.
**See under *Hemophilia and Other Bleeding Disorders*, p. 102.
***For SCOR concept, see p. 51.

role of different hemostatic components in the development and progression of occlusive arterial lesions may be evaluated and therapeutic agents may be tested.

- Complete clinical trials in progress on platelet antiaggregating agents. A major effort will be made to understand the actions of available pharmacologic agents and to develop new ones.

- Critically evaluate the role of laboratory platelet function testing in the study of experimental and clinical thromboembolic disease.

Schedule. Support for fundamental laboratory and clinical research will continue through FY 81. Specialized Centers of Research in Thrombosis have been reviewed and support will continue for successful centers through FY 80. Clinical trials will be initiated when these are indicated.

VENOUS THROMBOSIS

Program Background

As a result of past research, venous thrombosis, unlike arterial thrombosis, can often be effectively treated if diagnosed early. Prophylactic therapy is now possible, and detailed knowledge of the molecular mechanisms underlying the complex processes of hemostasis and thrombosis is increasing. However, the causes of various types of venous thrombosis are still poorly understood, and the existence and implications of the "hypercoagulable state" in these groups of disorders remain uncertain.

Program Goals

- The goals of this program are to refine our basic knowledge of venous thrombosis and to translate this knowledge into improved care.

Program Status

Purified circulating inhibitors of activated clotting factors have been isolated and their modes of action have been determined. It is now known why blood does not continue to clot once the process has begun. The most potent of the controlling factors is antithrombin III, the plasma heparin cofactor, whose activity dramatically increases in the presence of heparin, and acts against several clotting enzymes. Moreover, there is a familiar thrombotic disorder associated with an antithrombin III deficiency. However, the full significance of the antithrombin-heparin complex is not completely understood since the properties of heparin, which give it biological potency, remain a mystery.

Improved diagnostic accuracy for deep vein thrombosis has been achieved by the use of radioisotope-labeled fibrinogen given intravenously and monitored

at thrombotic sites with surface detectors. Noninvasive diagnostic methods employing ultrasound and electronically measured volume changes have also been valuable. Immunologic methods for the detection of fibrinogen fragments released during the coagulation process (fibrinopeptides) are in the development stage and show promise.

As many as 5,000 to 10,000 patients die each year in the United States from postoperative pulmonary embolism. A new type of heparin therapy, a low-dose prophylactic regimen, has been shown to be effective in preventing the development of deep vein thrombosis in high-risk patients. There is evidence suggesting that fatal pulmonary embolism is also prevented. The Institute, in cooperation with the American Heart Association, sponsored a workshop on recent advances in this complex subject which resulted in a useful book entitled Prophylactic Therapy of Deep Vein Thrombosis and Pulmonary Embolism.[11] This publication is being widely distributed and should lead to improved patient care.

Treatment of established thromboembolic disease revolves around heparin and the coumarin agents. Heparin is a polysaccharide of poorly defined chemical structure. The coumarin agents are vitamin K inhibitors, and it is now known that coumarin inhibits activation of coagulation proteins rather than produces a deficiency of these proteins. The Institute recently convened a conference involving polysaccharide chemists and investigators in hemostasis to encourage increased collaboration among workers in these fields. Conference proceedings will appear in the Federation Proceedings.

Fibrinolysins are also used therapeutically, but their status has not been established. Defibrinating agents--the most familiar example is the snake venom preparation, Arvin--have also been used to treat venous thrombosis.

Program Plans

Actions. The Institute plans to:

- Investigate factors responsible for development of venous thrombosis. Those factors associated with widespread risks, such as use of oral contraceptives, will be of special interest.

- Expand studies to determine the efficacy of additional noninvasive sensitive methods for diagnosis of thrombi. These methods should be economical, rapid, simple, and accurate.

- Develop laboratory tests which will identify patients at particularly high risk for development of thrombosis. Such tests may be based upon blood levels of inhibitors such as antithrombin III.

- Continue studies to define the chemical structure of heparin with a view toward synthesis. This work will lead to an understanding of the heparin-antithrombin cofactor role and possibly to improved results in therapy with heparin.

- Develop an adequate supply of standard, reference heparin to be used in laboratory investigations of the physical, chemical, and biological properties of heparin and to allow interlaboratory comparability of data.

- Support additional work on such practical unsolved problems as indications for instituting anticoagulant therapy, development of animal models for study of venous thrombosis, and clinical trials with new antithrombic drugs as they become availabe in acute thromboembolic disease.

- Complete clinical trials of heparin and platelet-inhibiting agents in patients undergoing hip surgery and disseminate the results.

Schedule. Fundamental laboratory and clinical investigation will be supported through FY 81. New clinical trials will be instituted when appropriate.

HEMOPHILIA AND OTHER BLEEDING DISORDERS

Program Background

Hemophilias A and B are lifelong bleeding disorders inherited through the female sex chromosome (X-chromosome). A total of approximately 25,500 persons in the United States have either hemophilia A or Hemophilia B severely enough to require treatment. These disorders are caused by a lack of factor VIII or IX of the clotting system. Individuals with these disorders and with rarer defects in other coagulation factors have repeated bleeding episodes throughout their lives that can lead to orthopedic, neurologic, medical, and psychosocial complications. Hemophiliacs place a requirement on the nation's blood resources far exceeding their proportion of the population. Von Willebrand's disease, another inherited bleeding disorder, is usually mild but may be even more common than hemophilias A and B.

Acquired disorders of hemostasis occur far more frequently than do the hereditary states. They afflict the newborn as well as the elderly, and they often arise as complications of various surgical and medical disorders.

Program Goals

- The major long-term research goal is a better understanding of the genetic and pathologic mechanisms underlying bleeding disorders.

- The immediate goals are to develop improved diagnostic techniques and specific treatments for hemorrhagic disorders.

- In the area of acquired coagulation disorders, an immediate goal is to develop better methods for detecting patients at risk, particularly surgical patients.

Program Status

Factor VIII is currently believed to be a large molecular weight protein made up of several subunits. Recent research has shown that while factor VIII is involved in both hemophilia A and von Willebrand's disease, the factor VIII antigen (the more antigenic component of the molecule) is present in hemophilia A, but is absent, decreased, or physically different in von Willebrand's disease. The defective component in hemophilia A (procoagulant factor VIII) is not itself an enzyme but appears to somehow regulate the enzymic activity of the clotting factors which are enzymes. Research has recently demonstrated that von Willebrand's factor can be synthesized by cultured vascular cells. This important finding should allow rapid progress in clarifying the structure and biological properties of this molecule. Von Willebrand's disease is, in fact, not one disease but a syndrome of variable expression of several distinct genetic abnormalities. Recent observations suggest von Willebrand's factor may play an important role in the genesis of atherosclerosis.

Important advances have been made in the therapy for hemophilia. Home treatment with plasma products is gaining wide acceptance. Because home treatment allows immediate therapy for bleeding episodes, it can retard or prevent many of the complications of this disorder. In one study, the incidence of joint complications in patients using home treatment was much less than that in another study involving patients on conventional treatment. Many complications of hemophilia therapy are now being recognized. Liver malfunction, hypertension, and other abnormalities have been reported and are the subject of further investigations. A recent workshop cosponsored by the NHLBI, the Food and Drug Administration, and the National Hemophilia Foundation considered these questions in detail.[12]

Inhibitors of factor VIII present a major problem. The NHLBI is currently seeking coordinated data on the origin and development of inhibitors in hemophiliacs. Significant progress has been made in purifying preparations containing factors II, VII, IX, and X which constitute the "prothrobin complex concentrates." The concentrates can be used in the treatment of patients with hereditary or acquired deficiencies of these factors. Although considerable attention has been directed to correcting the thrombosis occasionally attendant on the use of concentrates, this complication remains a problem. Several genetic variants of factor IX deficiency have been identified.

A variety of immunological tests for factor VIII have been developed that allow identification of women who carry the hemophilia trait. Female carriers do not exhibit the bleeding tendency. A very exciting new technique, measurement of the ratio of factor VIII activity and the amount of factor VIII antigen, appears much more reliable than measurement of factor VIII activity alone. The Institute is supporting a cooperative study with the National Hemophilia Foundation to determine the accuracy and reproducibility of this method of carrier detection.

The overall quality of life for the hemophiliac is a major concern. The cost of antihemophilic factors is often prohibitive to the patient. Side effects from treatment are frequently serious, and the psychosocial aspects of chronic bleeding conditions further complicate effective treatment of the disorder.

Information is incomplete on the geographic distribution, severity, mutation rate, morbidity, life expectancy, and mortality of the hemophiliac. Such information is essential to the development of a national blood policy because hemophiliacs are major, if not the largest, users of blood and blood products in this country.

Further data on the three-dimensional structure and biochemical function of the coagulation factors are needed. There is also a great need to study the mechanism of action of purified coagulation factors, particularly kinetic studies of their molecular interactions. Data from such experiments should provide an understanding of the critical factors for modulation and control of the total system.

Program Plans

Actions. The Institute plans to:

- Support research on the isolation, physical and chemical characterization, and definition of the biological role of von Willebrand's factor and its relationship to factor VIII-related antigen and procoagulant activity
- Determine the incidence and genetics of the different von Willebrand's syndromes and develop a test to identify asymptomatic carriers of von Willebrand's disease
- Define the possible relationship between von Willebrand's disease and atherosclerosis
- Further investigate the procoagulant principles in the prothrombin complex concentrate which are useful in treating patients with factor VIII inhibitors
- Promote research designed to assist practitioners in developing techniques for the management and prevention of systemic surgical bleeding complications and acquired bleeding disorders in both adults and children
- Support studies to characterize the coagulation defect in patients with uremia and liver disease and improve the treatment of these disorders; and support research attempting to develop an adequate substitution therapy in the bleeding tendency associated with hepatic failure.

Schedule. Clinical trials in factor VIII inhibitors will continue until 1978. Investigator-initiated fundamental research, developmental research on coagulation factors and their preparation, and workshops on the supply and use of antihemophilic factors will continue through FY 81. Development and testing of new and improved treatments will also continue through FY 81.

PLATELET DISORDERS

Program Background

The platelet plays a vital role in hemostasis. There are a variety of congenital and acquired platelet bleeding disorders which may result in mild to severe bleeding tendencies. Although acquired platelet deficiencies are most common, inherited platelet defects are more common than previously recognized. Recent research and new laboratory techniques have provided much new knowledge on platelet structure, biochemistry, and function. It is now possible to define accurately various inherited and acquired platelet disorders. This ability has greatly facilitated the clinical management of such disorders.

Program Goals

- The major goal is a better understanding of congenital and acquired platelet disorders which is necessary for the development of more effective therapy for individuals suffering from such disorders

- An additional goal is to increase the general understanding of the role of platelets in the mechanism of bleeding and clotting.

Program Status

The study of platelet clumping has allowed the identification of many drugs in common clinical use that can affect platelet function in vitro. Thus, the possible effect of such drugs in vivo can be predicted. For example, the biochemical site of action of the antiplatelet effect of aspirin has been partially defined. Aspirin binds to an enzyme that catalyzes the formation of platelet aggregating agents, the thromboxanes. In this way, aspirin inhibits platelet function, causes bleeding in some patients, and may act as an antithrombotic drug in others. Other physiological reactions between platelets and important metabolic constituents such as fatty acids and prostaglandins have also been clarified.

The platelet plasma membranes can now be isolated permitting characterization of the special properties of platelet membranes which enable them to act hemostatically. Purification of the major glycoproteins of platelets has led to the discovery of the molecular abnormality in two platelet disorders: Bernard-Soulier syndrome and Glanzmann's thrombasthenia.

Some patients with spontaneous platelet deficiency have been shown to have immunological disorders affecting the platelet membrane. With an understanding of these basic mechanisms, researchers are now able to devise useful clinical tests for these disorders. The role of the spleen in antiplatelet antibody production has been established and several serum tests to detect circulating antiplatelet factors are now available.

The recognition that after injury platelets release measurable materials such as platelet factor IV and B-thromboglobulin has led to the development of

assays now being studied for their usefulness in detecting increased platelet destruction, particularly in clotting. The use of the antibiotic ristocetin as an aggregating agent allows excellent discrimination among various platelet defects. Patients who exhibit increased platelet aggregation may be especially prone to the development of thrombotic atherosclerosis. Treatment with drugs known to inhibit platelet aggregation is under investigation.

The mechanism by which platelets adhere to each other and to the vessel wall is not yet understood. The role of platelets in thrombosis and atherosclerosis has enormous implications for public health--if indeed a method to prevent arterial thrombosis can be developed using platelet antiaggregating agents. Our knowledge of the mechanisms for biochemical control of platelet response to various stimuli or injury as well as characterization of the megakaryocyte (the parent cell of platelets), platelet production, and platelet maturation is quite limited but increasing rapidly. Further research in these areas holds the potential for significant new modes of treatment of platelet disorders. Impaired platelet function is a major component of von Willebrand's disease.* It is important to understand the interaction between factor VIII and platelets that leads to the adhesion defect characteristic of this syndrome.

Program Plans

Actions. The Institute plans to:

- Support studies to elucidate the mechanisms of biochemical control of platelet response to various stimuli or injury and also platelet production and maturation
- Support the development of methods for separating and culturing megakaryocytes to permit studies of patients with platelet defects
- Encourage the standardization of routine methods for laboratory platelet function testing and promote studies on the correlation between in vitro platelet function testing and in vivo platelet function
- Continue to support clinical trials of the effectiveness of thrombosis prevention by platelet-inhibiting drugs
- Develop animal models of platelet defects which will clarify the different platelet functions in relation to atherosclerosis and other diseases.

Schedule. Support of fundamental research on platelet biochemistry, physiology, and function; the role of platelets in bleeding and clotting disorders; and the development and testing of better treatments for platelet

*See under *Hemophilia and Other Bleeding Disorders*, p. 102.

disorders will continue through FY 81. A workshop on platelet function testing is scheduled in FY 77.

SICKLE CELL DISEASE

Program Background

Sickle cell disease (sickle cell anemia), a hereditary disorder characterized by painful crises, is a chronic anemia related to accelerated destruction of red blood cells and acute or chronic damage to various organs. It is an illness with symptoms that represent disorders in all body systems. The clinical manifestations are due to the presence of an abnormal hemoglobin (HbS) which aggregates within the deoxygenated red blood cells and causes them to assume a crescent or sickle shape. Sickled red cells are abnormally rigid and tend to stack up and cause a "log jam" effect, thereby occluding small vessels. This results in impaired circulation, tissue damage, and painful "crises." Equally important, sickle cell anemia has tremendous effects on the psychological makeup of the affected individuals. The primary defect in sickle cell disease is an amino acid substitution in a polypeptide chain of the hemoglobin molecule.

Program Goals

- A major program goal is to reduce the prevalence of and morbidity due to sickle cell anemia and to develop improved therapy for the sickle cell patient.

- The primary research goals are to increase fundamental understanding of sickled hemoglobin, the sickling process, rheology (blood flow), and complications of sickle cell anemia.

Program Status

Using advanced techniques, the hemoglobin S molecule is being further characterized. With a more complete understanding of the physical-chemical nature of the sickling process, it may be possible to develop ways of modifying the reaction at the molecular level that could then be applicable in vivo to the patient with sickle cell anemia. The current state of knowledge concerning the molecular aspects of sickle cell disease was summarized at a symposium held in December 1975.[13]

Studies of hemoglobin synthesis and its regulation in young red cells are being undertaken. Emphasis is placed on the synthesis of fetal hemoglobin in red cells because the presence of the more soluble hemoglobin F tends to prevent sickling. The ultimate goal is to increase synthesis of hemoglobin F in individuals with severe sickle cell syndromes in the hope that this may ameliorate the symptoms of the disease.

Drugs such as the ureas, alkylating agents, zinc, and cyanate can alter the hemoglobin S molecule in vitro in such a way as to reduce sickling. Clinical trials of urea showed this drug to be ineffective in vivo. Cyanate has been the most promising of these therapeutic agents and has received limited clinical

trial, but the neurologic toxicity produced with oral cyanate therapy precludes further clinical use by that route. The Institute sponsored a workshop to determine the feasibility of developing extracorporeal techniques to administer drugs that reduce the sickling of red cells but that are too toxic when administered orally. It is planned to publish the proceedings of this workshop. Accelerated efforts are required to develop effective antisickling agents to prevent the serious complications of sickle cell anemia.

Progress has been made in the antenatal diagnosis of sickle cell disease. Such diagnosis will improve as more refined instruments are developed to obtain samples of fetal blood.

The increased incidence of bacterial infections in patients, particularly children, with sickle cell disease has been examined. Studies of humoral and cellular immunity, the complement system, measurements of heat labile opsonins, and leukocyte function have shown that all these components are normal. Data are being collected on the natural history of sickle cell anemia to elucidate the large variations in clinical symptomatology found in this disease. These data will be useful in determining why the disease is much more severe in one patient than in another and why a crisis occurs.

Over the past three years, much information has been obtained particularly in the sickle cell centers concerning the clinical aspects of sickle cell disease. Included are studies on the nature of damage to organs such as the heart, kidneys, bones, and central nervous system. Improved methods have been developed for the diagnosis and treatment of eye complications. However, to provide more effective patient care, further detailed knowledge of the natural history of sickle cell anemia is needed to aid in the selection of specific modes of therapy.

Program Plans

Actions. The Institute plans to:

- Seek further information concerning the molecular nature of sickling and how it may be modified, and concerning the synthesis of sickle and fetal hemoglobin and how their relative production may be altered.

- Continue studies of the pathophysiology of the disease. While the major abnormality in sickle cell anemia is stasis of the red cells in the microvasculature, it is not yet possible to quantify this process.

- Continue efforts to develop an animal model which will allow investigation of the sickle cell phenomenon under conditions that more closely approximate the in vivo conditions of man.

- Seek further knowledge on the intermolecular contacts of the hemoglobin S fibers to provide a basis for the design of stereospecific antisickling agents.

- Develop extracorporeal techniques of administering drugs to circumvent the toxic effect of cyanate and other therapeutic agents.

- Develop an integrated study to collect uniform data on the natural history of sickle cell disease with the participation of the Comprehensive Sickle Cell Research Centers and independent investigators.

- Explore systematically the use of hypertransfusion therapy to prevent and treat crises. The improvement of the clincial course of the disease as well as the potential harmful effect of iron overload in transfused patients is of major concern.

Schedule. A broad integrated basic science and clinical research program conducted through investigator-initiated research grants, targeted research contracts, and Comprehensive Sickle Cell Research Centers will continue for the next five years.

DISORDERS OF THE RED BLOOD CELL

Of all the cellular components of the blood, the red cell has been most thoroughly studied. Its relative simplicity compared to other body cells has made it an ideal model for investigation of cellular metabolism and membrane function. It is the sole source of the hemoglobin molecule which is essential for oxygen transport. The strong basic research program in the red blood cell area has contributed not only to hematology but also to other scientific domains.

COOLEY'S ANEMIA

Program Background

Cooley's anemia (thalassemia), which affects thousands of persons in the United States, is a genetic disorder in which the ability to produce one of the polypeptide chains of the hemoglobin molecule is impaired, making the red cells very fragile. This reduces the life span of the red cells and results in severe anemia, bone thinning abnormalities due to the overgrowth of the inner marrow, impaired growth and development, and severe iron overload caused by blood transfusion therapy. Those afflicted require extensive care and seldom reach the age of 30. Those who inherit the trait for the disease become "carriers." Carriers are usually free of symptoms and generally enjoy normal health and a normal life-span.

Program Goals

- The major goal of the program is to find ways to prevent Cooley's anemia and to improve the treatment for those already affected by the disease through laboratory and clinical research. Included in this program is an effort to identify carriers of the trait through effective screening techniques.

Program Status

The clinical problem of Cooley's anemia (thalassemia) is a changing one. Recent research has further elucidated the molecular defects of thalassemia. In alpha thalassemia, deficiency of alpha-globin messenger ribonucleic acid (mRNA) results from the physical absence (deletion) of the alpha-globin gene. In contrast, in beta thalassemia, the beta-globin structural genes are present but are either inefficiently expressed or they encode mutant mRNAs that are degraded during development. Less commonly, beta thalassemia has been associated with gene deletion or with the presence of mutant, nonfunctional beta-globin mRNA.

Now that the molecular defects of Cooley's anemia have been defined and the advantage of maintaining by transfusion therapy has been established, the clinical problem of treating this illness is a changing one. Cooley's anemia requires frequent blood transfusions to sustain life. However, as a consequence of these transfusions, iron overload develops and has become the principal cause of death. There is a causal relationship of tissue iron overload to tissue damage. More frequent transfusions of patients have improved health and development during childhood, but tissue damage due to iron toxicity is the major health hazard to these patients. Iron binding compounds (chelators) increase iron excretion and thereby reduce the body's iron burden. Information is needed on how iron causes tissue damage and on the clinical effectiveness of chelation therapy. A suitable experimental animal is needed in which to conduct such studies.

Program Plans

Actions. The Institute plans to:

- Continue to support basic investigations into the molecular nature of Cooley's anemia and develop ways to modify the imbalance in globin chain synthesis through manipulation of the metabolic machinery of the cell

- Support research on the clinical management of the disease

- Continue to coordinate efforts with other institutes of the NIH and other federal and private agencies in support of basic and clinical studies in Cooley's anemia to develop improved methods of detecting the carrier state.

Schedule. Basic and clinical research will continue. Special emphasis will be given to the studies of clinical management of the disease during FY 77 and FY 78.

RED BLOOD CELL PRODUCTION (ERYTHROPOIESIS)

Program Background

Red cell production is under the control of the kidney hormone erythropoietin. Erythropoiesis is a model system for the study of cellular proliferation and has practical implications in the diagnosis and treatment of anemias. The anemia of renal disease, for example, is due predominantly to a failure of erythropoietin production.

Program Goals

- The primary goal of the program is the development of erythropoietin preparations for use in human disease; to use this hormone clinically, it is necessary to develop a pure erythropoietin for biochemical characterization.

Program Status

The action of erythropoietin on red cell production has been partially characterized. Information is accumulating concerning the site of erythropoietin production within the kidney and how production is regulated. Mouse hematopoietic cells maintained in long-term culture are being actively studied. Investigations of renal anemia continue with emphasis not only on erythropoietin production and iron balance but also on hemolytic mechanisms.

Collection and purification of human urinary erythropoietin is of the highest priority, because pure erythropoietin will allow the development of a more adequate clinical assay for this hormone. The purified hormone will also be useful in diagnosis and treatment of anemia. The role of factors other than erythropoietin insufficiency in the etiology of anemia of chronic renal disease is under study. The data obtained should help to devise more effective means to evaluate and manage this disease.

Program Plans

Actions. The Institute plans to:

- Continue the support of basic and clinical research on action and regulation of red cell production

- Support urinary erythropoietin collection and to continue the distribution of erythropoietin to investigators for purification, assays, and clinical trials.

Schedule. Support for fundamental research will continue. Search for additional urinary erythropoietin sources and supplies will be initiated in FY 77 and FY 78. New research directed toward the purification of erythropoietin will be initiated in FY 77 and maintained through FY 81.

APLASTIC ANEMIAS

Program Background

Aplastic anemia involves the failure of bone marrow stem cells (earliest parent cells) to reproduce. This failure causes anemia, bleeding, and infection due to the decreased production of blood cells by the bone marrow. Aplastic and refractory anemias are heterogeneous often fatal diseases of predominantly unknown origin, and their therapy is unsatisfactory because the basic underlying causes are not yet understood. At present, patients with aplastic anemia are treated largely by supportive therapy (red cells, platelets, antibiotics), by certain hormones and, more recently in suitable cases, by bone marrow transplantation.

Program Goals

- The major goal of the program is to improve the treatment of patients with aplastic anemias.
- A related goal is to obtain information concerning the natural history of these diseases.

Program Status

Techniques to produce colonies through special bone marrow cell culture have been developed to identify bone marrow hemopoietic stem cells in vitro. The culture techniques employed attempt to create conditions that simulate optimal conditions for bone marrow growth. Environmental factors in the bone marrow have been shown to affect the proliferation of stem cells, but most of these factors that influence the microenvironment are poorly understood. Although advances in bone marrow transplantation have offered limited success in the treatment and cure of selected patients, further understanding of the behavior of stem cells, the cause and the nature of their dysfunction, and of the natural history of aplastic anemia is required. New forms of treatment are being developed, but they are effective only in a minority of patients. Efforts should be directed toward indications for bone marrow transplantation and improvement in existing treatment.

Program Plans

Actions. The Institute plans to:

- Coordinate with other institutes of the NIH to support studies on the causes of aplastic anemia
- Support cooperating investigators to study the natural history of aplastic anemia and establish criteria for specific therapy.

Schedule. Investigator-initiated research on basic mechanisms in aplastic anemia will be supported during FY 77. Cooperative studies are planned for FY 78 through FY 81.

HEMOLYTIC ANEMIAS

Program Background

Metabolically active red blood cells maintain their hemoglobin in a functional state and their membrane integrity via complex mechanisms. A great variety of acquired and congenital disorders affect these mechanisms and thereby impair red cell function and survival. Patients with hemolytic anemia present difficult diagnostic and management problems. At the same time, these disorders provide unique opportunities to study cellular dysfunction in general.

Program Goals

- The primary goal of the program is to improve the health status of patients afflicted with any of the varied hemolytic anemias. This requires further elucidation of red cell membrane structure, function, and intracellular metabolism.

Program Status

Abnormalities of red cell membrane proteins have been identified and are considered responsible for at least one type of hemolytic anemia--hereditary spherocytosis. Other defects in red cell membrane structure and function involve exchange of electrolytes and changes in lipid function. In immune hemolytic anemia, identification and characterization of destructive antibodies is progressing, and their interaction with the red cell membrane is now better understood. Protein chemists familiar with the advanced techniques used to study membrane structure are needed for research in this area. In addition, studies in red cell metabolism would be strengthened through multidisciplinary approaches.

Program Plans

Actions. The Institute plans to:

- Continue the support of research on the chemical composition and function of the red cell membrane, including the metabolic events associated with red blood cells in normal and disease states

- Sponsor a workshop to bring together experts in the field of membrane chemistry and structure, including clinical investigators, biochemists, and biophysicists to exchange information on research into the structure-function relationships of the human red cell membrane in health and disease.

Schedule. Support for workshops to develop research approaches to elucidate the basic mechanism of hemolytic anemia is planned for FY 77 and FY 78. Plans developed from these workshops will be implemented during FY 78 through FY 81.

OXYGEN TRANSPORT

Program Background

The maintenance of an adequate oxygen supply is the most crucial phenomenon required for life. The red cell determines both the amount of oxygen which can be transported by the blood through its hemoglobin concentration and the oxygen available at any given oxygen tension by the affinity of its hemoglobin for oxygen. The interactions among the heart, lungs, and blood, which constitute the main ingredients of this supply system, are of particular interest to all divisions of the National Heart, Lung, and Blood Institute.

Program Goals

- The goal of this program is to increase the detailed understanding of how blood gases (oxygen and carbon dioxide) are exchanged throughout the body.

Program Status

Structure-function studies of human hemoglobin and hemoglobins of other mammals and invertebrates are in progress. Researchers conducting these studies are aided by the recent development of equipment for automatic rapid determination of oxygen hemoglobin equilibrium curves. The red cell is capable of regulating its own release of oxygen according to tissue needs. Beginning with the observation that 2,3-diphosphoglycerate interacts with the hemoglobin molecule to modify its oxygen affinity, a variety of studies have clarified the general behavior not only of this phenomenon but also of other interactions which modulate the function of hemoglobin. Provided the metabolic activities of the cell are intact and substrates such as glucose and inorganic phosphate are available, the cell will respond to an increased amount of deoxygenated hemoglobin by increased glycolysis and thereby an increase in 2,3-diphosphoglycerate. The net result is enhanced tissue oxygen delivery.

Oxygen deficiency and its clinical management continue to be major concerns of the Institute. While a sound program of basic research exists, there is need to sponsor additional work at the clinical level--particularly work involving interdisciplinary laboratories where the capabilities of diverse disciplines may be brought to bear on this complex problem. This field provides an opportunity as well as a need for cooperation among the three divisions of the NHLBI.

Program Plans

Actions. The Institute plans to:

- Continue studies on mechanisms of control of oxygen exchange and hemoglobin
- Attempt the development of in vivo studies of oxygen exchange at the capillary level in experimental animals and in man.

Schedule. Fundamental and clinical research will continue. Efforts during FY 77 and FY 78 will emphasize in vivo studies of oxygen exchange.

BLOOD RESOURCES

In recent years, the need for blood transfusion has expanded at such an accelerated rate that blood has now become a scarce and essential resource. Previously hospital-based functions--the recruitment, collection, and processing of blood--are increasingly being centralized at large regional blood centers which pool resources, provide training and research programs, and make economic and high quality services available to all. This growth in the volume and complexity of transfusion therapy has created a new discipline involving scientists, physicians, allied medical personnel, administrators, engineers, and a burgeoning commercial industry. The rapidity of growth has presented some challenging problems in basic, developmental, and clinical research. A serious need to develop new systems for the management and organization of the blood service complex also exists. In recent years, the Institute has been given a mandate to stimulate and support innovative changes in blood banking. Resulting efforts have produced substantial benefits in many phases of research, development, and organization of the blood resource.

The Institute's research accomplishments and goals relevant to blood resources will be discussed in five areas: nationwide blood system, safety of blood therapy, blood component therapy, blood substitutes, and transplantation biology.

NATIONWIDE BLOOD SYSTEM

Program Background

Dissatisfaction with the existing blood service complex stimulated the definition of a National Blood Policy to improve blood services by developing a well-coordinated, integrated, and efficiently managed blood service system. As it was thought that such a system should not be managed by the federal government, the American Blood Commission (ABC), a private organization, was created in 1975 to implement the goals of the National Blood Policy.

The blood service organizations, along with consumer and labor groups, health insurance companies, and others, serve as members of the ABC and operate on a cooperative and voluntary basis. The Institute, because of its commitments to blood banking and research in hematology, was designated as the focus for studies into the science and management of the nation's blood resources.

Program Goals

- The primary goal of this program is to foster the efficient use and assure an adequate supply of high quality blood and blood products.

- The establishment of a national blood resource information system essential for effective planning is one of the immediate needs as well as a long-range goal.

Program Status

The Institute's greatest challenge in the blood resources area, which it shares with the ABC, is the implementation of the National Blood Policy. This policy emphasizes the efficient management of the national blood resources, and this poses research problems new to the NHLBI. Two of the most important goals in this endeavor are the establishment of an all-volunteer blood donor system and the development of a national blood data system.

In addition to assisting in the creation of the ABC, the Institute is supporting research conducted by ABC task forces in the following areas: The Regional Association of Blood Banks, The National Blood Data Systems, The Committee on Commonality (charged with the development of standard and machine-readable labels for blood products and of other automated methods), and Donor Motivation.

The Institute has recently established a National Research and Demonstration Center in blood resources. This Center is mainly concerned with improved acquisition, processing, storage, distribution, and clinical use of blood and blood products.

With the Bureau of Biologics (BoB) of the Food and Drug Administration (FDA), the Institute sponsored a workshop to explore the possibility of regional licensure of blood services. A working paper has resulted from this effort.

A working conference on health behavior was organized by the NHLBI at which a multidisciplinary group of 50 expert consultants and 22 Institute staff members investigated in depth many diverse behavioral aspects of interest to the NHLBI. A major topic of consideration included in the proceedings of this meeting was motivation of the voluntary blood donor.[14]

A completed study oriented toward regionalization[15] of blood banking describes the dynamics of 12 regional blood supply systems. It emphasizes their similarities and differences with respect to mode of operation, effectiveness, and efficiency. The resulting publication is being widely disseminated.

A survey of personnel needs in blood banking sciences was initiated jointly with BoB/FDA. This study will identify personnel needs and make recommendations for training programs. The resulting data will be very useful in NHLBI planning.

The Institute has continued to participate in the US-USSR Cooperative Program in Blood Transfusion.*

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*See under *PROGRAM COORDINATION*, p. 162.

Program Plans

Actions. The Institute plans to:

- Continue to support the ABC task forces in their efforts to implement the National Blood Policy
- Continue to support the establishment of a national blood resource information system in collaboration with BoB/FDA and to work toward a comprehensive National Blood Data System
- Sponsor programs to train the personnel needed to collect, process, and distribute the national blood resources
- Continue to support the US-USSR Cooperative Program in Blood Transfusion.

Schedule. The Institute will continue to support the ABC task forces on Regionalization, Commonality, National Blood Data System, and Donor Motivation through FY 77. The Institute will also continue to collaborate with BoB/FDA in the establishment of a blood resource data system known as the Blood Establishment Inspection and Registration System (BEIRS).

SAFETY OF BLOOD THERAPY

Program Background

Transfusions play an important role in the saving of lives. However, transfusion of blood and blood products may produce serious infections, toxic reactions, or accidents due to mismatching. These complications remain at a disturbingly high level indicating the need for effective carrier detection tests, improved methods for the removal or inactivation of infectious agents from blood, development of bioinert, nontoxic substances for surfaces in contact with blood, and error-proof identification of samples.

Program Goals

- The principal goal of the program is to prevent morbidity and mortality from posttransfusion hepatitis and other transfusion-transmitted infections.
- A second important goal is to eliminate toxic substances from the many surfaces contacted during the collection, processing, storage, and infusion of blood.
- A third goal is to produce a universally acceptable positive-sample patient identification system and to eliminate human errors through the development of automated blood typing and cross-matching instrumentation.

Program Status

An Institute-sponsored evaluation of the impact of hepatitis B antigen screening of donors has shown that hepatitis B virus is responsible for a decreasing number of the posttransfusion hepatitis cases currently observed. Non-A, non-B agents are now more common causes for transfusion-associated hepatitis disease, the incidence of which remains high. Reduction of the risk of posttransfusion hepatitis remains a major challenge. The greatest current need is for a test to detect asymptomatic viremia in blood donors. In the meantime, work will continue on a method of removing hepatitis viruses from all blood products. Such removal could prevent morbidity and mortality. Equally urgent is the need for epidemiologic studies to help develop methods of control. The problem of health care personnel carrying the hepatitis virus is of concern. Parameters of infectivity and of transmissibility must be established, and carriers for appropriate study of these parameters (i.e., transmitters and nontransmitters) must be identified epidemiologically.

Epidemiologic studies have shown that oral spread is a significant method of transmitting hepatitis and that genetic factors appear to contribute toward the carrier state. The Institute sponsored four studies intended to evaluate the prophylactic ability and treatment potential of hepatitis B immune globulin (HBIG). Results so far have been ambiguous. Recommendations and guidelines for HBIG use are still under consideration. HBIG may prevent the transmission of hepatitis B virus from mother to child across the placenta; this possibility is under investigation.

Five major medical centers are jointly studying transfusion-associated hepatitis. It is planned to apply presently available and newly proposed tests for detection of carriers to all donors, and to give tests for etiologic diagnosis to the recipients. In this study to date, almost all cases of hepatitis can be classified as non-A, non-B disease. A primate research facility is being supported to provide colony-bred, antibody-free chimpanzees for research related to viral hepatitis.

Studies of transfusion-transmitted cytomegalovirus and toxoplasma have indicated that these agents produce disease only in special groups. Materials are currently being collected to evaluate other agents, potentially transmitted by transfusions--for example, slow viruses.

The major source of serious transfusion errors is not technical but clerical. Reduction of clerical errors, perhaps by a fail-safe system to identify the donor, the blood unit, and the patient, is urgently needed to insure that the right blood gets to the right patient.

There is great interest in the interactions of blood with the many surfaces it may contact during the transfusion process. For example, some plasticizers are capable of leaching from containers into transfusion products. Studies are underway to evaluate the effects of one group of such substances, phthalic acid esters, on the recipients of transfusions. Additional research is needed in this and related areas.

Program Plans

Actions. The Institute plans to:

- Support the development of assay methods that will permit the serologic identification of carriers of non-A, non-B hepatitis
- Continue epidemiologic and clinical characterization of non-A, non-B hepatitis
- Support development of methods for removing hepatitis and other viruses from plasma derivatives
- Search for bioinert, nontoxic substances for surface contact with blood
- Search for instrumentation, automation, and new methods for typing, cross-matching, and other blood banking procedures.

Schedule. Basic and applied research on infections and toxic reactions to transfusion will continue. Support in both areas through investigator-initiated research grants and targeted research contracts is expected to increase though FY 78 and level off through FY 81.

BLOOD COMPONENT THERAPY

Program Background

Blood is an organ composed of three basic cellular elements (red blood cells, white blood cells, and platelets) suspended in a fluid medium (plasma). The demand for red blood cells sets the pace for the collection of whole blood. About 70 percent of all transfusions involve patients needing only the red blood cells, yet whole blood is still used in the majority of transfusions. Reducing the use of whole blood not only constitutes good medical practice but also increases the availability of blood components which are often in short supply. Adhering to the principles of blood component therapy is critical in the management of this most precious national resource--blood.

In recent years, the demand for platelet transfusions has increased as a consequence of intensive treatment of malignant disorders and the advent of new therapeutic measures such as bone marrow transplantation. Unfortunately, current techniques limit the preservation time for platelets to less than 72 hours, thus limiting the availability and supply of platelets for transfusion.

Granulocytes, a type of leukocyte (white blood cells) are important in fighting and preventing infection. Patients with certain malignant diseases have low white blood cell counts (granulocytopenia) either as a result of their disorder or as a side effect of therapy. Granulocytopenia makes these patients particularly susceptible to infections, and despite the use of antibiotics, their mortality from infections is extremely high. Leukocyte replacement therapy for

granulocytopenic patients with infections was first attempted over 20 years ago, but not until recently were the methods developed to procure adequate numbers of white cells for effective transfusion therapy.

Immunohematology is the study of the many aspects related to blood group factors. The modern transfusion era began 75 years ago with the discovery of the major blood groups (A,B,O), and although many new blood groups have been discovered since then, the methods and techniques employed have changed little. Results obtained by the manual methods currently used are highly variable, and the reagents used in most blood banks are relatively unstandardized. Blood groups are important in blood transfusion, but the primary biologic significance of these groups has never been identified, particularly in relation to diseases.

The improved therapy resulting from recent research has placed increased demands on the preparation of clinically useful fractions of human plasma. An even greater demand for plasma proteins will occur in the future. The recovery of new products from plasma and an improvement in the yield of existing products can make a profound impact upon the usage of the national blood resource. With the increased frequency of intravenous administration of plasma proteins, the incidence of allergic reactions caused by sensitization to structural variations in proteins will rise. The genetic influence on these structural variations must be understood to permit expanded transfusion therapy.

Program Goals

The program goals are to:

- Determine and clarify parameters of collection and function related to effective transfusion of platelet concentrates, white blood cells, red blood cells, and soluble plasma fractions
- Define clearly optimal storage conditions for maximum preservation of platelets, white blood cells, red blood cells, and other plasma fractions
- Clarify guidelines to maximize the efficient use of blood components
- Advance the technology of blood banking procedures for typing and cross-matching red blood cells
- Improve methods for plasma fractionation so that biologically active components such as antihemophilia factors can be purified in sufficient quantity and without contamination by the hepatitis virus
- Develop a preparation of gamma globulin, an important plasma protein for defense against infections, which can be safely administered intravenously

- Isolate and test new but presently unused plasma fractions which are of potential clinical usefulness, and improve understanding of the genetic differences in plasma proteins.

Program Status

Most patients treated with repetitive platelet transfusions become refractory to platelets obtained from random donors because of isoimmunization (sensitization) to histocompatibility (transplantation) antigens. Therefore, a number of clinical studies dealing with problems of sensitization to histocompatibility (HLA) antigens are being undertaken. Feasiblity studies, employing platelet concentrates from donors matched to recipients for HLA antigens, strongly suggest that such therapy is possible and effective. To focus attention on these problems, the Institute sponsored a workshop at the National Research and Demonstration Center in Seattle which resulted in a publication entitled Single Donor Platelet Transfusions: Scientific, Legal, and Ethical Considerations.[16] Results from studies of short-term liquid preservation and long-term cryopreservation (freezing) of platelets have now defined the conditions for their effective storage in the liquid state for three days. This is a beginning, but much remains to be learned concerning the collection, storage, processing, and transfusion of platelet concentrates.

The viability of granulocytes is such that they must be transfused soon after procurement. Thus, the inability to preserve these cells has limited their use. In addition, the procurement of adequate numbers of granulocytes for transfusion is time-consuming, requires specialized techniques and equipment, and also demands a high degree of donor cooperation.

In collaboration with the National Cancer Institute (NCI), the NHLBI is developing a comprehensive research program aimed at procurement, storage, and clinical transfusion of granulocytes. Studies to develop methods for both long-term storage of granulocytes and research dealing with transplantation antigens and their significance have been supported by the Institute as well as other institutes at the NIH. However, further extensive research is needed on donor compatibility and the procurement, metabolism and function, storage, and clinical aspects of transfusion therapy of granuloctyes.

With proper preservation, red cells of rare blood groups can be stored for emergency use. As noted above, frequently whole blood is transfused when only red blood cells are needed. This practice is wasteful, and even with optimal storage, will continue to lead to blood shortages; thus, the medical community needs to be instructed on proper transfusion practices. For optimal storage of red blood cells, their level of 2,3-diphosphoglycerate (2,3-DPG) must be maintained. Effective preservation also requires the maintenance of a closed sterile system. Special sterile connecting devices that are inexpensive and easy to use have now been developed. They allow for the closed separation and washing of thawed red blood cells thereby extending the red cell shelf life.

New methods to fractionate blood plasma and to isolate and test new products resulting from such fractionation are being developed. A clinical trial of the effectiveness of the intravenous administration of gamma globulin is now in progress. A workshop on the utilization of albumin, the major plasma protein, as a therapeutic agent was jointly supported by the Institute and the

BoB/FDA. Proceedings of the Workshop on Albumin[17] have been published and widely disseminated. Work is currently underway to automate the large-scale fractionation procedure for continuous isolation of plasma proteins. The development of chromatographic techniques for fractionation shows promise for isolation of antihemophiliac factor on a large-scale basis. Other methods are being developed to obtain purified preparations of minor protein fractions (e.g., human antithrombin III, alpha-1-antitrypsin, and ceramide trihexosidase).

The National Blood Policy calls for optimal utilization of blood and blood products. Blood plasma contains many factors which can be used to treat patients with hemophilia, immunodeficiency syndromes, or high risk of infection (newborns, burn patients, or cancer chemotherapy patients). However, at present, certain plasma fractions are not utilized. Further work is required to develop large-scale fractionation techniques. The availability of larger quantities of minor plasma components will permit more extensive basic research on their structure and function as well as clinical research in new areas. Greater knowledge of the structure of the plasma components will help to solve the problem of allergic reactions to transfused proteins.

In summary, it will be necessary to develop clearer indications for the use of blood components and better methods to assess their effectiveness. In addition, methods must be improved for blood separation and preservation so the many important components can be recovered fully and economically. Lastly, there is great practical need to advance the technology and methodology of red cell immunohematology.

Program Plans

Actions. The Institute plans to:

- Define the present clinical use of platelet concentrates, explore the indications for their transfusion, and develop better methods to assess their effectiveness
- Continue studies characterizing the sensitization and other problems that occur in association with platelet transfusion therapy
- Continue to develop improved, efficient, rapid, and safe methods to collect and store platelets
- Encourage basic research to characterize the changes that occur in platelets during collection and manipulation to further define optimal conditions for prolonged preservation of these cells
- Initiate leukocyte transfusion studies to evaluate clinical indications, dose requirement, frequency of administration, prophylactic usage, and possible deleterious effects of leukocyte transfusion therapy
- Explore leukocyte donor safety for both long-term and short-term effects

- Explore bioengineering approaches to improve the methods of leukocyte procurement to maximize cell yield and functional integrity
- Continue studies on long-term and short-term storage of granulocytes
- Continue to evaluate the clinical significance of 2,3-diphosphoglycerate red cell preservation
- Support research to establish criteria for standardization of blood bank reagents and for automating blood typing procedures
- Encourage studies related to the clinical significance of red blood cell groups
- Conduct clinical trials of sterile connecting devices
- Continue research on the production of clinically useful plasma protein fractions in order to improve yield and safety and reduce the cost of existing products
- Support the development of new techniques for recovery of protein fractions some of which are discarded in the current fractionation procedure
- Support clinical trials to facilitate licensure of intravenous administration of gamma globulin
- Support the study of molecular and genetic structure of plasma proteins
- Support the investigation of molecular alterations which may permit utilization of plasma proteins from species other than man.

Schedule. Clinical studies of many aspects of platelet transfusion therapy will continue. Basic and applied research will be supported by a request for investigator-initiated studies with implementation during FY 77. The collaborative white blood cell research effort initiated with the NCI in FY 76 will continue through at least FY 79. Preservation studies will continue during FY 77. Activities in the areas of red blood cell research will continue during the next five years. The development and testing of new processes for continuous plasma fractionation will continue. As the processes are perfected and implemented, these activities should become self-supporting. At that time, the level of basic and clinical research on the structure, function, and immunologic variation of plasma components can be increased.

BLOOD SUBSTITUTES

Program Background

Blood substitutes have a tremendous potential value in health care. Once developed to the point of human use, the preparations could reduce the hepatitis problem as well as supplement and conserve the natural blood supply. Blood substitutes would be invaluable in times of acute shortage or widespread disaster, particularly if natural blood were unavailable.

Program Goals

- The major goal of this program is to support the development of a safe and effective blood substitute.

Program Status

The Institute sponsored the 1974 workshop on Artificial Substitutes for Blood to identify the use of various synthetic and natural compounds as blood substitutes. The proceedings were published in the Federation Poceedings.[18] Subsequently, studies to develop and test new blood substitutes were initiated.

Animal transfusion studies using blood substitutes have been highly encouraging. Primates have been maintained for several hours with up to 80 percent of their blood replaced with a synthetic-type substitute (a perfluorochemical).

Other animals have been maintained for longer periods with 90 percent of their blood replaced with a cell-free hemoglobin solution which constitutes a natural-type substitute. Significant results have been observed in animals that have been completely transfused with this natural-type substitute. The animals completely recover from the transfusion and continue to live normal lives after replacing the blood substitute with their own blood. However, much additional basic and applied research is essential to develop safe, effective, and clinically useful blood substitutes.

Program Plans

Actions. The Institute plans to:

- Continue studies designed to synthesize and screen new perflourochemical-type substances for use as blood substitutes

- Continue to support studies to synthesize and test different types of blood substitutes such as chelates and to evaluate methods for their administration.

Schedule. Support for the synthesis of perfluorochemicals for use as artificial blood subsitutes has been recently initiated and will continue. The support of a study to standardize the preparation and testing of cell-free hemoglobin solutions is planned. Studies of this type are anticipated to continue for at least five more years.

TRANSPLANTATION BIOLOGY

Program Background

The Institute encourages and supports research in transplantation biology including areas such as histocompatibility, rejection, immunology, and immunogenetics. Since transplantation resources overlap with the blood banking system, the importance of combining tissue and organ banks with blood banks in implementing an effective transplantation system is recognized.

Program Goals

- The major goal of the program is to advance basic understanding of the transplantation process to improve clinical application.

Program Status

The NHLBI and other institutes at the NIH--for example, the NIAID--have contributed to studies rapidly advancing the knowledge base in the area of transplantation biology. Such studies have included basic understanding and relevance of transplantation (HLA) antigens for renal and bone marrow transplantation and platelet and granulocyte transfusion. For example, the Institute provided partial support for the second annual meeting of the American Association for Clinical Histocompatibility Testing in April 1976.

Expansion and further development of the knowledge of the major histocompatibility system in relation to transplantation and transfusion must be continued. Additional studies to prevent transplant rejection due to prior sensitization of the recipient are needed. Continuation of clinical studies to improve platelet and white blood cell transfusion is required. Special attention to organ preservation and transplantation is needed. A determination of the feasiblity of regional blood centers participating in tissue typing and storage functions needs to be made. A particular need will be the establishment of regional, national and/or international registries for donor selection and evaluation of results of transplantation programs.

Program Plans

Actions. The Institute plans to:

- Continue to support research in the broad area of transplantation biology
- Explore the possible role of regional blood centers in collection, processing, and distribution of human tissues and organs for transplantation
- Support appropriate platelet and granulocyte transfusion studies*

*See *Blood Component Therapy*, pp. 118-19.

- Establish and maintain registries of potential tissue and organ donors
- Support a bone marrow transplantation registry to help evaluate this new treatment modality*
- Maintain strong interinstitute collaboration in transplantation biology.**

Schedule. Studies related to transplantation will continue through FY 81. The International Bone Marrow Transplant Registry will be administered and supported by the Institute in collaboration with the NCI through at least FY 79.

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*See *Aplastic Anemias*, pp. 111-12.
**See *PROGRAM COORDINATION*, p. 149.

V.
PREVENTION, EDUCATION, AND CONTROL PROGRAMS

Bioscientists in the United States lead the world in pushing back the frontiers of ignorance concerning man in health and disease. However, if our hard won understanding is to improve the health of the nation, it must be translated with utmost speed to fight disease, and where applicable, it must be rapidly applied to prevent disease or delay its onset. The potential payoffs envisioned to result from the implementation of effective prevention, education, and control (PEC) programs are substantial. Perhaps of even greater importance than the financial gains resulting from effective PEC programs is their potential to delay significantly the onset of disease and thereby decrease pain and anguish and improve the quality of life. Education of both professionals and the public, coupled with high individual motivation, can lead to changed life styles which may ultimately lead the way to prevention of many diseases, or at least to a considerable delay in their onset. With this philosophy in mind, the Congress mandated the National Heart, Lung, and Blood Institute (NHLBI) via the Heart, Lung, and Blood Act of 1972 (PL 92-423) to initiate active PEC programs. This mandate was restated and amplified in the renewal of the Act in 1976 (PL 94-178).

The Office of Prevention, Education and Control (OPEC) was established to coordinate PEC programs throughout the Institute. The OPEC has initiated and/or conducted projects in continuing medical education. It has acquainted Institute staff with the capabilities of behavioral and social sciences in resolving health behavior problems, and it has stimulated research relative to the Institute within the behavioral and social science communities. As a result of the initiatives undertaken by this new office, a bridge has been established that has facilitated new multidisciplinary approaches in the attack on heart, lung, and blood diseases.

Since its creation in 1948, an important mandate of the Institute has been to inform and educate the general public and health professionals. Over the years, the NHLBI has carried out its educational activities through a variety of mechanisms. This educational task is of considerable magnitude. During FY 76, twenty-five press releases and announcements addressed to the communications media were developed and distributed to lay, medical and health press, broadcasters, associations and societies, health educators, and other pertinent constituencies, and the Institute responded to approximately 63,700 direct requests for information. Last year, 94 publications, ranging in scope from book-sized reports and symposia proceedings to pamphlet and fact sheets were developed, produced, issued, and promoted by the NHLBI, and in response to specific inquiries, over 1.3 million copies of various publications were distributed. A catalog listing of all NHLBI publications is prepared twice a year for distribution to health educators and libraries, as well as in response to inquiries. As a result of an analysis of 1,086 requests for information received over a three-month period, fact sheets were prepared on a number of subjects of special public interest including hyperlipoproteinemia, cardiac extrasystole, venous thrombosis and pulmonary embolism, and congestive heart failure. In response to requests from congressional appropriations committee staff, the Institute prepared Congressional Special Reports on the state of the art and recent research advances in six major disease categories: hemophilia, coronary heart disease, black lung disease, emphysema and chronic bronchitis, sickle cell disease, and high blood pressure. Exhibits for use at professional society and lay group meetings are also available. In FY 76, exhibits on the NHLBI intramural activities, lung disease, sickle cell disease, and hypertension were scheduled and/or staffed.

In an effort to expand information/education resources, the Institute has established through the Assistant Director for Prevention, Education, and Control an informal exchange system between the NHLBI and its grantees and contractors involved in centers and clinical trials programs. Cooperative efforts have been undertaken to develop written and audiovisual materials required by these programs.

The Institute works in tandem with public information components of the professional societies and voluntary health associations. The goal is to communicate to the public the basic and clinical research activities in heart, lung, and blood diseases and resources supported and conducted by the National Heart, Lung, and Blood Institute.

Other activities not previously undertaken by the Institute include the development of "state-of-the-science" information resources in such areas as: (1) nonpharmacologic approaches to the treatment of hypertension, (2) expansion of the behavioral/educational consultant roster, and (3) a visiting scholar program for behavioral scientists with interests in health-related problems to foster cooperation with other institutions outside the NIH that shape mutual educational and behavioral concerns.

HEART AND VASCULAR DISEASES

In order to provide physicians and related health personnel with the most up-to-date information in the area of cardiovascular diseases, coordination of federal agency efforts and voluntary and professional organizations has been a major goal. Thus, many PEC activities have concentrated on multidisciplinary collaborations with an exchange of information across several fields of specialization.

In the area of patient and public health education, the focus of activity has been on studies relating to motivational and educational approaches and techniques which result in short-term and long-term adoption of positive behavior leading to improved health.

Special emphasis is currently placed on the testing and evaluation of programs for the prevention of two particular cardiovascular disorders--hypertension and arteriosclerosis. Since a substantial body of knowledge exists which could significantly reduce morbidity and mortality related to these two conditions if implemented and widely applied, long-range research and demonstration programs in the prevention and control of hypertension and arteriosclerosis have been a major priority. Further special efforts will be directed toward studies which focus on issues such as psychosocial determinants of health behavior, educational strategies for maintaining the health of children and adults, and influencing the behaviors of health care providers to enhance the quality of care rendered.

ARTERIOSCLEROSIS

Program Background

As described in the research section of this report, arteriosclerosis is a silent, slowly developing disease which results in heart attack, stroke, and peripheral vascular disease. While much remains to be learned, a number of factors that increase risk of developing atherosclerosis and coronary heart disease have been established. These include elevated blood lipids, high blood pressure, and cigarette smoking. These risk factors can be modified, and health professionals and the public should be encouraged to adopt health habits that reduce these risk factors.

Clinical trials are now in progress to determine the extent to which intervention upon the three primary risk factors--smoking, high blood pressure and high blood lipids--can yield reductions in morbidity and mortality from cardiovascular diseases.* For individuals at high risk who seek to reduce their risk factors, information and education on how to achieve this goal should be made available. Preventive measures may involve steps to reduce risk factors through dietary

*See under *ARTERIOSCLEROSIS*, p. 50.

modifications and changes of personal habits and life style which must be followed for prolonged periods. This will require improved methods of intervention, greater education and motivation of health professionals and the general public, as well as an increased understanding of the psychosocial aspects of arteriosclerotic disease. Both the health professionals and the public need to know how risk-factor reduction can be achieved.

Program Goals

- A continuing program goal is to reduce disability and death from atherosclerotic disease of the heart, brain, and blood vessels through the prevention and control of risk factors.

Program Status

A staff analysis of needs in relation to prevention, education, and control activities in cardiovascular diseases is in the planning stage. Staff and advisory committees will review the scientific base currently available in several disciplines such as medicine, cardiology, psychology, sociology, anthropology, and education which have relevance to prevention, education, and control activities related to cardiovascular illnesses. Priorities will be established and recommendations will be made for future activities.

Research has continued in several areas involving risk factors in cardiovascular disease. These include methods of lowering blood lipid concentrations through programs in dietary education and psychosociological deterrents to smoking among school children. Studies are also in progress relating to changing dietary patterns to reduce blood lipids in high-risk individuals and their families.

Nutritional staff at the Institute have continued to work with university groups and with the American Heart Association to develop ways to promote nutrition education. Institute nutritionists are also increasingly called upon to participate in professional education programs sponsored by voluntary and official agencies.*

The National Research and Demonstration Center in Cardiovascular Diseases in Houston, Texas, is conducting programs designed to increase the awareness of high school and college students and their families concerning risk factors that increase atherosclerosis and its sequelae, coronary heart disease and stroke, and the means for their reduction. Studies are being undertaken to deter the initiation of smoking by young people and to encourage cessation or modification of smoking in those who already have the habit. In other projects, educational and behavioral interventions are being tested to determine their effectiveness in lowering elevated serum cholesterol levels of the general population.

A Specialized Center of Research at Stanford University in California recently investigated the effectiveness of a media campaign versus a media campaign reinforced with counseling for improving personal health habits. The study

*See under *PROGRAM COORDINATION*, pp. 153-54.

focused on three major risk factors for coronary heart disease--high blood pressure, high blood lipids, and smoking.

Recently, the National Heart, Lung, and Blood Institute sponsored four conferences on the application of behavioral science to cardiovascular problems. Four publications have resulted from these conferences. [19,20,21,22] A directory has been developed for the use of staff consisting of behavioral and social scientists with interest and expertise in conducting research related to cardiovascular disease.

The US populace consumes large quantities of commercially prepared convenience foods. The exact contents of these products change frequently and therefore are under constant analysis. Data tables giving the nutritive content of a standard portion are being prepared. These tables will provide the necessary information to enable compliance with the special diets which have been developed for the treatment of the various hyperlipidemias. Nutrition education and diet counseling in the treatment of hyperlipidemias remain areas of high Institute priority.

A major challenge for the future will be to devise systems to screen and identify individuals at risk in an easy, rapid, and cost-effective manner, and to discover ways to educate and motivate high-risk persons to change those habits and life styles which have been demonstrated to increase their susceptibility to atherosclerotic disease.

Program Plans

Actions. The Institute plans to:

- Encourage the development of models for the practice of preventive medicine in relation to cardiovascular disease to be utilized in the education of health professionals

- Develop, evaluate, and apply dietary survey and counseling methods, and contribute to the compilation and distribution of updated food composition tables including commercially processed foods

- Encourage studies to determine the most effective educational strategies for young children and adolescents that will assist them to adopt health behavioral patterns conducive to risk-factor reduction.

Schedule. It is anticipated that risk-factor reduction studies will continue and that dissemination of information on risk-factor detection and prevention will be expanded in FY 77 as data become available. A broader range of multidisciplinary consultants, including consumers, will be sought to assist the Institute in the coming years in its educational activities relating to prevention of arteriosclerosis, hypertension, and stroke.

HYPERTENSION

Program Background

The National High Blood Pressure Education Program (NHBPEP) was established in 1972 to increase public and professional awareness of hypertension, including its frequency in the population and the benefits of its early detection and therapy. This important program is coordinated by the NHLBI.

The National High Blood Pressure Education Research Program (NHBPERP), an outgrowth of the NHBPEP, supports educational research to explore cost-effective ways to achieve a greater degree of blood pressure control in hypertensive patients. This program is supporting behavioral research in health education, attitudes, motivation, and compliance as they relate to the prevention and treatment of hypertension. A research effort to identify effective education methods which will increase hypertensive patient adherence to therapy is also in progress.

Program Goals

- The major goal of the NHBPEP is reduction in morbidity and mortality from hypertension through education.
- A continuing national goal of this program is to expand public and professional knowledge of the dangers of high blood pressure and the effectiveness of early detection and treatment.
- Another goal is to make the most up-to-date knowledge of the clinical management of hypertension available to specialists and general practitioners and to bring under effective, long-term antihypertensive therapy all persons who have severe or moderately severe high blood pressure.

Program Status

Since its establishment, the National High Blood Pressure Education Program has enjoyed the support and cooperation of approximately 150 national voluntary and professional organizations, some 15 federal agencies, numerous community organizations, and virtually all state health departments. Eleven research projects are currently underway to help develop better approaches to educating hypertensive patients.

There is encouraging evidence that the public education program of the NHBPEP is gradually achieving one of its goals--the motivation of individuals to have their blood pressure checked. In 1971, the Health and Nutrition Examination Survey conducted by the National Center for Health Statistics indicated that 49 percent of Americans who had high blood pressure were unaware of their condition. As shown in Figure 4, a survey of fourteen community-based populations in 1974 indicated that the number of persons unaware of their hypertension had dropped to 29 percent and that the number of hypertensive individuals achieving good blood pressure control had almost doubled--rising from 16 to 29 percent

of the hypertensive population. The two surveys, although not exactly comparable, do suggest that the coordination of effort brought about through the National High Blood Pressure Education Program has increased the proportion of the population having their blood pressure checked and of those who are adhering to a blood pressure lowering regimen.

These data are supported by the fact that patient visits for hypertension and hypertensive heart disease have increased by 50 percent since the advent of the program. First visits have risen over 40 percent. As illustrated in Figure 5, during the same period, visits for all causes and first visits for all causes rose only about 14 percent.

The National High Blood Pressure Education Program achieved a significant step this year toward unifying the nation's hypertension control effort. Previous efforts had been hampered by varying recommendations from several sources on approaches to detection and treatment of high blood pressure. Through its High Blood Pressure Coordinating Committee and a special task force, the NHBPEP has been able to develop a single national consensus embodied in "The Joint National Committee Report on the Detection, Evaluation and Treatment of High Blood Pressure."[23] The report represents agreement among many major organizations including the American College of Cardiology, the American Academy of Family Physicians, the American College of Physicians, the American Heart Association, the American Medical Association, the National Kidney Foundation, the National Medical Association, the Veterans Administration, and the United States Public Health Service.

The report on detection, evaluation, and treatment of high blood pressure emphasizes that detection is only part of the problem; getting a person under treatment and continuing that treatment is a greater task. Groups or individuals who plan to measure blood pressure must insure an adequate system for repeating blood pressure measurement to confirm elevations and for prompt referral of persons with elevated pressure. The report states that screening efforts should continue, but if all physicians and dentists regardless of specialty would measure blood pressures routinely, the need for mass screening efforts would be greatly decreased.

Summary recommendations include the following:

1. Virtually anyone with a diastolic pressure of 105 mmHg or more should be treated with antihypertensive drugs.

2. For persons with a diastolic pressure between 90 mmHg to 104 mmHg, drug treatment may or may not be necessary.

3. Only a few, inexpensive tests are needed to properly evaluate most people with high blood pressure. Hospitalization is rarely needed.

4. A simple, "stepped-care" approach to drug treatment should be used. Dosages, side effects, and contraindications are outlined.

Late in 1976, the National High Blood Pressure Education Program conducted a National Conference on Hypertension Control in the Work Setting. Although recent progress has been achieved in this area, the Institute felt that greater emphasis should be placed on high blood pressure control in the work environment. Business has invested millions of dollars and has made progress toward reducing industrial hazards and accidents; yet, for each person dying of these causes, more than fifty in the age range of the work force die from cardiovascular disease. Key leaders from business, industry, management, labor, and interested representatives participated in a one-day session to assess the status of blood pressure control programs at the worksite. A working group is being convened from the participants of the conference to assist the Institute's efforts in promoting high blood pressure control. This group will act as a resource to labor and management representatives when requested by providing models for care that are cost-effective and by maintaining contact with participants to keep attention focused on this major problem.

The Institute supports the Hypertension Detection and Follow-up Program (HDFP), one of the largest studies of the treatment of persons with high blood pressure ever undertaken. The HDFP is a community-based program designed to assess the value of early detection and vigorous treatment of persons with all levels of high blood pressure. In 1973 and 1974, some 158,900 persons in 14 communities across the United States had their blood pressures measured in their homes or work places by HDFP staff members. About 10,940 persons were found to be hypertensive by a two-stage screening process and they were enrolled in the program. One impressive finding of the initial screening was an apparent marked improvement in the level of detection, treatment, and control of high blood pressure in this program as compared with earlier population surveys. As indicated above, these findings may reflect the impact of recent national and local programs emphasizing the importance of high blood pressure as a risk factor for cardiovascular disease.

Treatment for hypertension is lifelong, must be individualized, and it may have side effects. Therefore, a major challenge is developing a therapeutic alliance between the patient and his physician which will facilitate the patient's adherence to therapy. Building such a physician-patient alliance requires a greater understanding of personal and societal attitudes toward hypertension and long-term treatment than most physicians currently possess. To accomplish this, additional emphasis is required on both educational and behavioral research. It is also important to develop simplified treatment regimens and to provide easier access to the health care system. The continuing development of regional and community structures will assist in making pertinent information available to the public and to health professionals, as well as in facilitating screening, detection, and treatment in the local communities.

Program Plans

Actions. The Institute plans to:

- Continue to increase public knowledge of the dangers of high blood pressure and the benefits of effective treatment through the National High Blood Pressure Education Program, its High Blood Pressure Information Center, the public media

and education programs for consumers, health professionals and patients, the Community Development Service, and community action projects where communities assume responsibility for their own high blood pressure control programs.

- Continue an education research program to develop new knowledge and educational techniques that will increase awareness of hypertension, promote health education, and provide improved methods of assuring patient adherence to treatment.

- Initiate education and behavioral research related to the Hypertension Detection and Follow-up Program* to characterize and evaluate differences in knowledge, attitudes, and behavioral patterns between persons with high blood pressure who participate fully in hypertensive therapy and those who participate poorly.

- Study models of community high blood pressure control programs in selected areas. This will involve the development of evaluation methodology in terms of community organization, cost benefits, morbidity and mortality reduction, and comparison of quality of care in public and private clinics. Such programs should also evaluate ways in which nurses, pharmacists, and other health personnel can assist in providing long-term follow-up for persons who require antihypertensive therapy. Focus will also be on work settings as sites for detection and treatment.

- Plan a new survey of public knowledge and attitudes regarding blood pressure. This will provide a follow-up to the Harris Survey conducted in 1972 and a benchmark for programs in public education on high blood pressure.

Schedule. Activities related to control, education, and demonstration in hypertension will continue to receive strong emphasis in FY 77 and will require ongoing support at the present level until effective prevention and control are achieved. Initial results from the current education-intervention studies and demonstration projects now underway will be assessed in FY 77 and FY 78. Application of promising techniques and approaches will take place beginning in FY 78 and will occur for several years beyond. The number, variety, and distribution of public and professional educational materials will continue to expand for the next several years, as will community consultation services. Program evaluation and monitoring techniques will receive emphasis in FY 77 in order to assess the impact on the public and on health professionals of health education and intervention techniques now under study. The impact of possible new legislation broadening the approach to hypertension control is being assessed, and the role and focus of the High Blood Pressure Education Program will be adapted to contribute most effectively to any such expansion.

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*See under *Hypertension*, p. 56.

CORONARY HEART DISEASE

Program Background

About 4 million persons suffer manifest coronary heart disease, and their survival, productivity, and comfort depend in part on their understanding of this disease, on their following medical advice, and on their health behavior and life style. Improved professional and patient education and skills in behavior change are important to effective control. About 400,000 deaths occur annually from coronary heart disease prior to hospitalization. Therefore, prevention and care of sudden cardiac events are major problems requiring improved emergency care systems and better public and professional education on how to prevent and respond correctly to cardiovascular crises.

Once a heart attack or other serious cardiac illness has occurred, both the rate of return toward normal functioning in society and the completeness of this return may remain inadeqate unless the disability can be minimized and recovery hastened. This requires appropriate attention to the medical and behavioral factors associated with cardiac rehabilitation and prevention of recurrence.

Program Goals

The Program goals are to:

- Introduce the latest developments in emergency care for the cardiac patient into comprehensive emergency care systems
- Encourage the development and evaluation of innovations in the education of health professionals, cardiac patients, and the general public covering steps to avoid and to respond to cardiac emergencies
- Encourage the development of improved educational approaches for the professional, the patient, and the public concerning the nature of coronary heart disease and its management.

Program Status

Improvement continues in our understanding of the fundamental underlying causes of sudden cardiac death, the means for its early treatment, and even its prophylaxis.* New information has been incorporated into emergency care systems. Using the best available emergency cardiac care, one community of half a million (Seattle, Washington) has saved in excess of 100 lives per year which would otherwise have been lost as the result of heart attacks.

Numerous Institute programs such as the Multiple Risk Factor Intervention Trial (MRFIT), the NHBPEP, and several clinical trials encourage the adoption of more healthful behavior in persons at risk of coronary heart disease to

*See under *Coronary Heart Disease*, p. 62, and *Arrhythmias*, p. 66.

prevent such disease. These programs attempt to intervene upon elevated blood pressure, elevated blood lipids, obesity, and smoking by improving the health consciousness of their participants. Similar heightened consciousness of positive health behavior aids persons who already have recognized coronary heart disease.

A report issued last year by the Institute's Task Force on Cardiac Rehabilitation called for provision and expansion of rehabilitation services.[24] Follow-up discussions with experts in many related disciplines have been held and Institute staff are continuing to refine these recommendations in order to provide a sound basis for the development of a realistic and effective program. The National Research and Demonstration Center at Dallas is also carrying out continuing medical education in the area of cardiovascular disease.

Program Plans

Actions. The Institute plans to:

- Continue to contribute, in collaboration with other federal agencies, to the design and analysis of the cardiac elements of emergency care systems, emphasizing the implementation of research developments cited elsewhere in this report under Actions in the Research Section on Coronary Heart Disease

- Encourage research and demonstration projects for professionals, patients, and the general public in procedures that attempt to prevent cardiovascular emergencies and to promote appropriate responses to cardiovascular emergencies.

- Explore, in collaboration with the Social and Rehabilitation Service, the establishment of demonstration programs for the rehabilitation of patients with cardiovascular disease.

Schedule. Current studies and demonstration projects on decreasing the delay between the onset of symptoms and the seeking of medical care will continue in FY 77 and FY 78. As sound data and information are obtained on the effectiveness of various techniques of educating the public to recognize heart attack symptoms and to seek medical care, the more promising techniques will be considered for application in a wider range of geographic and social settings. Continuing development of more rapid and comprehensive emergency care systems will provide opportunities in FY 77 and FY 78 for improvements in the cardiac elements of such emergency systems. Progress in this area is to a large extent contingent on activities of other agencies with responsibilities related to the broader area of emergency medical care. Similarly, activities and progress in the wider area of health-related prevention, control, and education will provide approaches and techniques applicable to programs focused on coronary heart disease.

CONGENITAL HEART DISEASE

Program Background

Recognition of congenital heart disease may be particularly difficult in the critically ill newborn infant. Yet, this is the period during which many deaths occur from congenital heart disease, and several thousand lives can probably be saved annually by early recognition of cardiac problems in the newborn.

Program Goals

- The goals are to develop techniques for the early recognition of cardiac disease in the newborn and to initiate demonstration programs for early recognition and treatment of congenital heart disease.

Program Status

Important advances in the recognition, interhospital communication and transport, and management of the newborn infant with respiratory distress have taken place. Many aspects of this system are also applicable to the early recognition and improved management of congenital heart disease.

Continuing investigations and the development of a variety of diagnostic techniques (for example, ultrasonic imaging) are providing capabilities for more accurate assessment of congenital heart disease. These new methods are being used for earlier recognition of congenital heart disease in the newborn infant. The development of new methods of medical and surgical treatment of young infants necessitates a cadre of highly trained personnel. Specialized groups to deal with cardiac problems are needed throughout the health care delivery system. Regionalization of personnel and facilities is advocated because of the expertise and expensive equipment required.

Program Plans

Actions. The Institute plans to:

- Introduce techniques of early recognition and management of congenital cardiac disease into programs for the early management of respiratory distress in the neonate to more efficiently utilize communications, transport, technical facilities, and trained personnel common to the effective management of both programs.

Schedule. Exploration of actions in this area will start in FY 77 through the Task Force on Heart Disease in Children. Program implementation will be influenced by the Task Force Report.

LUNG DISEASES

Program Background

The prevention, education, and control programs of the Division of Lung Diseases draw upon research findings that are ready to be used beyond major medical centers. Demonstration and education programs are fostered to bring research information to physicians and other health professionals who are concerned with health at the community level. Where appropriate, information is also disseminated for the education of the public in general, and of patients with lung diseases in particular.

Program Goals

- The goals of these programs are to utilize demonstration and education projects to bring to appropriate target groups--practicing physicians, other health professionals, educators, and the public--information about the causes of lung diseases, their prevention, and alleviation or cure that can be utilized at the community level to improve public health.

Program Status

Educational programs have been initiated at five institutions utilizing the latest research progress in recognition and treatment of neonatal respiratory distress syndrome (NRDS). These programs are directed to physicians, nurses, physician assistants, midwives, and other professionals in prenatal care, delivery, and neonatal care in urban or rural settings. The prevention of risk of respiratory distress is emphasized through proper care before and during birth, and through early identification and treatment of the infant in respiratory distress.

Educational programs concerned with early treatment of acute respiratory insufficiency in the adult are under way at three institutions. These programs are directed to professional and nonprofessional personnel who are likely to be the first contacts of patients suffering from this disorder.

Four other institutions are designing and evaluating prototype continuing education programs addressed to well-defined areas of pulmonary medicine and to problems encountered by the nonspecialist community physician in office or hospital practice. Procedures to motivate the physician to take advantage of the available education resources and procedures and to evaluate the impact of such education on the quality of patient care are being stressed.

In addition, the Institute supports the Lung Research and Demonstration Center at the University of Vermont. Initiated in December 1974, this Center coordinates the activities of several groups: the State Department of Health, the Vermont Lung Association, and participants from university departments of community medicine, continuing medical education, pathology, physiology, psychology, and epidemiology. The prevention, control, and education program presents special problems because it requires the mutual interest and cooperation

of experts from disciplines that only rarely work together. The cooperative activities at the Vermont Lung Center indicate that it is possible to develop a prevention, education, and control program that will draw upon many segments of professional communities and will reach a variety of target groups.

The Institute has convened a special Task Force on Prevention, Education, and Control in Respiratory Diseases to recommend a comprehensive long-range plan targeted at specific pulmonary diseases which may be prevented or controlled through educational interventions. This task force met for the first time in February 1976 and since then has worked with many other experts to develop its report. The task force and its task groups include experts from many fields and disciplines: pulmonary, industrial, and community medicine; epidemiology; health professional and public health education; behavioral science; economics; and communications. It is anticipated that the report of the task force will provide guidelines for the stepwise development of a cohesive and well-designed program which until now has not been available for this facet of activities in lung diseases.

Program Plans

Actions. The Institute plans to:

- Identify research advances that are potentially applicable to the prevention, diagnosis, or treatment of specific respiratory diseases and are ready to be communicated beyond a major medical center
- Identify specific target groups that can be helped through demonstration or education projects
- Foster the development of demonstration or education projects that include evaluative procedures to assess the efficacy of the intervention
- Initiate projects to determine the magnitude of the respiratory disease problem in the United States in terms of incidence, prevalence, and case fatality rates for each of the disease categories; and to determine risk factors for these disease categories
- Initiate intervention experiments to quantify the therapeutic effect of smoking cessation and other life style changes on chronic bronchitis and emphysema
- Continue its educational efforts in fibrotic and immunologic lung diseases with particular emphasis on prescreening and placement of workers in industry to avoid hazardous environmental agents.

Schedule. In the coming year, the Institute will complete and publish the findings of its Task Force on Prevention, Education, and Control for Pulmonary Disease. This document will outline the issues which will be of primary concern to the Institute in this area for the next 10 years. In addition,

the Institute will continue and expand its effort to quantify the effects of smoking cessation on chronic bronchitis and emphysema. In a new initiative, the Institute will explore the effects of patient education on the incidence and severity of asthmatic attacks in children.

BLOOD DISEASES AND BLOOD RESOURCES

A primary goal of the Institute is to support demonstration projects which bridge the gap between the validation of a new research finding and broad implementation in the health care arena. The current programs in the areas of blood diseases and blood resources in which prevention, education, and control activities are being undertaken are sickle cell anemia, Cooley's anemia, hemophilia, thromboembolic disorders, and blood resources.

SICKLE CELL ANEMIA AND COOLEY'S ANEMIA

Program Background

The emergence of health education as a priority in the maintenance of health and prevention of illness has played a major role in the development of specific efforts directed toward better understanding of sickle cell anemia, Cooley's anemia, and other hemoglobinopathies (red cell disorders). There is a great need to provide a clear distinction between sickle cell anemia and sickle cell trait. Education and counseling programs designed to disseminate accurate information and to foster a better understanding by the public are supported through the Sickle Cell Clinics and the Comprehensive Sickle Cell Centers.

Program Goals

- The primary goals are to increase awareness and understanding about sickle cell disease, Cooley's anemia, and other hemoglobinopathies through the initiation and expansion of education and information programs for the community, medical, and allied health personnel; and to demonstrate accurate techniques for diagnosis, and appropriate and sensitive approaches to genetic counseling.

Program Status

Pilot studies have been initiated for a program of education, screening, and counseling for individuals with Cooley's anemia.

Sickle Cell Screening and Education Clinics continue to provide a service for the dissemination of information and dispelling of myths about sickle cell anemia and sickle cell trait. Specific protocols have been developed to assure accuracy of information and to aid in the evaluation of educational materials utilized in screening programs.

A permanent exhibit on sickle cell anemia has been established in the Health Sciences Section of the Chicago Museum of Science and Industry. This inclusive

exhibit portrays many aspects of the "Sickle Cell Story" including the molecular characteristics, evolution of scientific knowledge, origin and distribution of the HbS gene, symptomatology and mechanisms of genetic transmission. The exhibit was developed as a portion of the public education program of the Comprehensive Sickle Cell Center at the University of Chicago.

Accurate diagnostic techniques have been demonstrated for both routine screening and advanced methods for identifying hemoglobinopathies. Federal programs are monitored for quality control through a proficiency testing program which has resulted in accurate definitive diagnoses. The Institute has coordinated educational efforts with other Federal agencies for more effective utilization of available resources.

Experts in the area of genetic counseling were convened to emphasize the nondirective approach to counseling and to establish criteria for evaluation of the effects of genetic counseling. Demonstration models to provide screening, education, and counseling services have been established through a variety of institutions and organizations.

The Institute initiated regional workshops on sickle cell anemia through nongovernmental organizations and established an Information Resource Center, thereby increasing the availability of educational resources to many communities.

The First National Sickle Cell Educational Symposium was held in May 1976 to present current clinical, scientific, and educational information to physicians, paramedical personnel, health educators, and health workers in the field of sickle cell disease. This was done through analyses of case study presentations and workshops on the basic techniques in education, genetic counseling, and clinical management. The proceedings of this symposium will be published.

Despite the above efforts, currently only a small segment of the population has been reached through the existing network of screening, education, and counseling programs. Clearly, designs for more innovative programs are needed that will reach a wider segment than the "at-risk population." A major challenge will be to find better ways of involving and informing health professionals and employers.

Program Plans

Actions. The Institute plans to:

- Continue collaboration with other Federal agencies in the development of effective programs for the dissemination of accurate information about sickle cell anemia, Cooley's anemia, and other hemoglobinopathies. Specific activities in testing, counseling, and education have been authorized under Title IV of PL 94-278 for implementation by the Bureau of Community Health Services (BCHS) and the NHLBI. Coordinated efforts will assure comprehensive approaches to these problems and will avoid unnecessary gap, overlap, and duplication.

- Support a comprehensive education program to provide the public and health professionals with up-to-date, accurate

information on sickle cell anemia and trait, Cooley's anemia, and other hemoglobin disorders.

- Support projects which focus on the psychosocial aspects of these disorders with emphasis on evaluating the effects of genetic counseling.

- Expand efforts to develop programs for education, screening, and counseling in Cooley's anemia.

Schedule. Support for the development and expansion of education programs should increase, and efforts will be initiated to evaluate the impact of demonstration activities.

HEMOPHILIA AND OTHER BLEEDING DISORDERS

Program Background

Hemophilia and other bleeding disorders cause a considerable amount of morbidity and are a significant drain on the nation's blood resource. With the enactment of PL 94-63,* the Department of Health, Education, and Welfare (DHEW) was directed to support the treatment of hemophilia. While administration of this new initiative was vested in the Health Services Administration (HSA), the Institute served as a consultant and took into consideration the complexity of hemophilia as well as the limited size of the program in formulating some recommendations, citing the need for: (1) a definition of the comprehensive care concept in the treatment of hemophilia, (2) educational and training functions at the treatment centers, and (3) more information about hemophilia and the opportunities to obtain such data from the treatment centers.

When applications for hemophilia centers were received by the HSA, the Institute assisted in their review. Seventeen centers were ultimately funded and the NHLBI continued to serve in a scientific consultant capacity.

Program Goals

- The overall goal of the prevention, education, and control programs in this area is to assist in the translation of new research findings to the medical community, the patients, and the general public.

Program Status

The Institute has taken steps to assist in educating the medical community, to help resolve complex research problems, and to offer scientific expertise to those concerned with the delivery of medical care.

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*This is the Health Revenue Sharing and Health Services Act of 1975 which provides for the establishment of hemophilia programs including the establishment of comprehensive hemophilia diagnostic and treatment centers.

In cooperation with the National Hemophilia Foundation (NHF), the Institute sponsored a laboratory workshop to demonstrate the accuracy of new techniques for carrier detection. Laboratory studies have revealed that carriers of hemophilia could be identified more accurately with new techniques employing immunologic tests coupled with knowledge of the coagulation characteristics of the blood. The results of this demonstration will be published and widely disseminated.

A book summarizing the established knowledge about the care of hemophilia was compiled by the Institute, in cooperation with the National Hemophilia Foundation.[25] The book is intended for use by medical and paramedical personnel.

The Institute will continue to assist with the rapid dissemination of new information to the medical community and the lay public, and to cooperate with the National Hemophilia Foundation and other appropriate organizations in this effort.

Program Plans

Actions. The Institute plans to:

- Cooperate with the HSA in the implementation of the treatment center legislation
- Evaluate the requirements for blood resources as they might be changed by the establishment of special programs and comprehensive hemophilia diagnostic and treatment centers by the HSA in response to PL 94-63
- Stimulate data collection on the clinical care of hemophilia from existing and future sources
- Support education and demonstration programs dealing with production, economic, and logistic aspects of the antihemophilic factors.

Schedule. In FY 77, hemophilia treatment centers will be established as an ongoing program. Data collection will begin, and evaluation of needed blood resources will be performed.

THROMBOEMBOLIC DISORDERS

Program Background

In recent years the development of methods to prevent deep vein thrombosis and pulmonary embolism has provided a particularly fertile field for education and prevention activities.

Program Goals

- The primary goal of this program is to identify and promote education and prevention activities in the area of deep vein thrombosis and pulmonary embolism.

Program Status

The Institute has carefully monitored clinical studies on prevention of deep vein thrombosis and pulmonary embolism. Planning meetings, a workshop, and publications have been sponsored to bring the necessary information to the attention of the medical community. Major clinical trials, many of these in Europe, were carefully followed by the Institute. A workshop held in conjunction with the American Heart Association was convened to evaluate the data regarding prophylactic therapy of deep vein thrombosis and pulmonary embolism.[26] The workshop proceedings have been widely disseminated. Educational efforts by professional organizations have been stimulated as a result of these Institute activities. The Institute will continue to present accurate and critically analyzed data on these disorders to the largest audience with a minimum of delay.

Program Plans

Actions. The Institute plans to:

- Assist appropriate organizations in presentation of the most modern methods of diagnosis and therapy relevant to thromboembolic disorders
- Continue to evaluate and critically analyze the data regarding preventive therapy and make the results available to the medical community
- Sponsor a workshop on the role of platelet function testing in the diagnosis of hemorrhagic and thromboembolic disorders.

Schedule. The development and implementation of education programs aimed at the appropriate use of antithrombotic therapy will be continued through FY 81. A workshop on platelet function testing will be held in FY 77.

BLOOD RESOURCES

Program Background

The Institute's Blood Resources and Transplantation Program is financing studies to improve methods of collection, preservation, and processing of blood and blood products. Of particular importance are the Institute's efforts in support of the establishment of an all-volunteer blood donation system through the support and development of public education programs focusing on motivating blood donors.

Program Goals

The program goals are to:

- Achieve effective management of the nation's blood resources
- Aid in the establishment of an all-volunteer blood donation system through effective donor motivation
- Prevent posttransfusion hepatitis through screening donors and educating physicians.

Program Status

The National Blood Policy was developed to assure an adequate supply of high quality blood for all. The Institute is supporting research carried out by the task forces of the American Blood Commission (ABC) relating to this purpose. Of particular concern are studies on donor motivation and studies preparatory to a National Blood Data system. This system will have a major impact on planning and education in the use of blood resources. A number of workshops have been held to develop guidelines on the improved use of blood and blood products.

In a step toward education of physicians in the proper use of albumin, the major plasma protein, the Institute cosponsored a workshop on the use of albumin as a therapeutic agent and coordinated the development of guidelines for its clinical use. The proceedings of the workshop were published.[27]

A National Research and Demonstration Center dealing with education and demonstration has been established at the Puget Sound Blood Center in Seattle, Washington. A major objective of the center is to develop demonstration projects designed to validate new management techniques in the blood resource area. Educational materials for professional groups are being developed as part of this effort. More than 100 existing educational materials have been selected for review and detailed evaluation. New educational materials for medical student and physician education on component therapy in blood banking are in the final stages of review. Once validated, these and other educational materials will be exhibited at national meetings of blood bank professionals for further evaluation.

Program Plans

Actions. The Institute plans to:

- Continue to support research by the ABC task forces for the purpose of bringing about the optimal utilization of blood and blood components through the establishment of an all-volunteer blood donor system, regionalization of blood supply systems, and the development of a national blood data system
- Continue to support the National Research and Development Center in the development of educational materials to meet the information needs of the public and professionals involved in health care

- Continue to support a program designed to prevent posttransfusion hepatitis. There is a need to keep physicians informed about the known potential infectious hazards of transfusing of blood and blood derivatives.

Schedule. The development, evaluation, and implementation of education programs will continue and will focus on the safe and optimal utilization of blood and blood products, the cooperative studies and implementation of uniform resources data systems, and the programs to detect, remove, or prevent hepatitis.

VI.
PROGRAM COORDINATION

The National Heart, Lung, and Blood Institute (NHLBI), as part of its responsibility to provide leadership to the National Program, continues to coordinate those aspects of all federal health programs and activities related to heart, blood vessel, lung, and blood diseases, and blood resources. In affecting coordination, the Institute's efforts are facilitated by an informal but effective communication and collaboration network among federal health agencies and by a formal legislated mechanism--the Interagency Technical Committee (ITAC) on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources. There are also numerous programs in progress that involve nonfederal agencies and institutions working in collaboration with each other and/or federal agencies. Examples of formal and informal coordination and collaboration (both federal and nonfederal) are presented in this chapter. In addition, many of the prevention, education, and control projects described in Chapter V involve significant collaborative efforts.

INTERAGENCY TECHNICAL COMMITTEE

The Interagency Technical Committee was established in 1972 in accordance with Section 416 of the Public Health Service Act as amended by PL 92-423. The IATC was charged with assuring the adequacy and technical soundness of the National Program. The IATC was also given the responsibility for providing full communication and information exchange on programs and activities related to the National Program. The Director of the NHLBI serves as chairman of this committee which includes all federal departments and agencies with health functions or responsibilities. Departments and agencies represented on this committee are shown in Table 11.

Table 11. MEMBERS OF THE INTERAGENCY TECHNICAL COMMITTEE

AGENCIES OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE	OTHER DEPARTMENTS AND AGENCIES OF THE FEDERAL GOVERNMENT
Alcohol, Drug Abuse, and Mental Health Administration	Department of Agriculture
Center for Disease Control	Department of Defense
Food and Drug Administration	Department of Transportation
Health Resources Administration	Energy Research and Development Administration
Health Services Administration	Environmental Protection Agency
National Institutes of Health	National Aeronautics and Space Administration
Social and Rehabilitation Service	National Science Foundation
Social Security Administration	Veterans Administration

Collaborative interaction and coordination among member departments and agencies are based on a framework of varying needs and circumstances. Prominent among them are the following:

- The need and desirability to obtain specialized information, advice, or services not presently available within the NHLBI or one IATC member agency or department
- The need to have access to a resource of, or a population studied by, another agency
- The existence of a problem whose solution calls for skills and viewpoints in addition to those present in the NHLBI
- The traditional and natural tendency for health researchers to communicate informally regardless of their organizational affiliations
- The need to respond to mandates from the executive and/or legislative branch of government.

Many major collaborative efforts exist between the NHLBI and federal and nonfederal organizations. Examples of such have been included in detail in ITAC reports describing federally supported programs related to the National Heart, Blood Vessel, Lung, and Blood Program.[28]

During the past year, the IATC has moved to increase interagency coordination and collaboration by increasing its activities and expanding active involvement from agency administrators and policymakers to agency program managers who function at operational levels. Accordingly, interagency working groups have been established around specific heart, blood vessel, lung, and blood problem areas. These working groups convene at scheduled workshops to discuss

specific aspects of a problem area. Highlights of particular programs and projects are discussed, mutual problems are identified, technical advice is provided, and opportunities for coordination and collaboration are examined. Recommendations for continuing coordination or implementation of new collaborative initiatives are developed by each interagency working group and presented to the IATC membership.

In addition to informal cooperation by the NHLBI and other agencies, formal agency working groups have been established and are active in the areas of high blood pressure screening, pediatric pulmonary disease, and sickle cell disease education.

High Blood Pressure Screening

The Interagency Working Group on High Blood Pressure Screening, using the Federal Employee Health Program existing in several federal agencies, has examined various models of hypertension screening programs. The problems and progress of these programs have been discussed and methods of program improvement have been explored. In addition to the exchange of technical and administrative programmatic information aimed at effective interagency utilization of positive aspects of existing screening programs, several specific actions have resulted from these discussions. These actions include the following:

- The NHLBI supplied education and screening materials to 266 Health Services Administration (HSA) health units across the country, to 10 major National Aeronautics and Space Administration (NASA) centers and component institutions, to the Department of Transportaton (DOT), to the Health Resources Administration (HRA), and to the United States Air Force (USAF).

- The NHLBI provided impetus to federal agencies' participation in National High Blood Pressure Month activities resulting in an overall increase in participation nationwide.

- The NHLBI utilized the expertise of other federal agencies in planning the Conference on Hypertension at the Work Site, thus insuring a broader interest base in the conference.

Pediatric Pulmonary Diseases

Several opportunities for NHLBI collaboration with other organizations are being explored by the Pediatric Pulmonary Diseases Working Group. Some of these include:

- Potential collaboration with the HSA in states where the NHLBI is supporting pediatric pulmonary research and the HSA Maternal and Child Health Service Programs support activities involving crippled children

- Possible establishment of communication links between the NHLBI Pulmonary Specialzed Centers of Research and HSA's Pediatric Pulmonary Centers

- Continued joint support with the National Institute of Arthritis, Metabolism, and Digestive Diseases of projects in cystic fibrosis.

Sickle Cell Disease Education

The Interagency Working Group on Sickle Cell Disease Education initiated a communication network among eight federal agencies aimed at promoting exchange of information and thereby enhancing collaboration at the state and local levels in the area of sickle cell education. This communication is geared to maximize the use of components of existing programs such as sickle cell centers and clinics, Job Corps centers, vocational rehabilitation centers and Veterans Administration (VA) hospitals, and to enhance the delivery of educational services to a larger segment of the population. A major objective of the working group is to identify areas of overlap and duplication, and to develop recommendations for interagency coordination and collaboration. The educational program is being carried out by the Screening and Education Clinics of the HSA, the NHLBI's Comprehensive Sickle Cell Centers, and the National Sickle Cell Education Program. The educational objectives of the program are:

- To provide accurate information about sickle cell anemia and sickle cell trait to the general public in order to correct misinformation and dispel myths
- To educate medical and allied health professionals regarding the problems of sickle cell anemia
- To increase the awareness of the "at-risk" population.

OTHER FEDERAL AND NONFEDERAL COORDINATION

The Institute views its coordination mandate seriously as indicated by the fact that it had nearly 50 reimbursable agreements with other federal agencies in FY 76. Some of these agreements involve interdivision or interprogram coordination while others involve federal agencies, nonfederal organizations, professional societies, or elements of the private sector. Examples of efforts, wholly or partially supported by the National Heart, Lung, and Blood Institute, are summarized below.

Emergency Medical Services

The Secretary of Health, Education, and Welfare established an Interagency Committee on Emergency Medical Services, with the Division of Emergency Medical Services, Bureau of Medical Services, Health Services Administration in the lead role. The Associate Director for Cardiology, Division of Heart and Vascular Diseases, NHLBI, represents the National Institutes of Health on the Interagency Committee. Within the context of the National Program, the NHLBI is responsible for the elucidation of the pathophysiology of heart disease in its earliest emergency phases and for the development of methods of care suitable for incorporation into emergency medical care systems.

The NHLBI has collaborated with the Division of Emergency Medical Services on topics of mutual interest and importance, including cosponsorship of the Second National Conference on Emergency Health Services and of the Meeting on Cardiopulmonary Resuscitation sponsored by the American Red Cross and the National Science Foundation.[29]

Artificial Heart Research

From the inception of the Artificial Heart Program in the early 1960s, the NHLBI and the Energy Research and Development Administration (ERDA) have collaborated to determine the feasibility of an artificial heart and to exchange technical information. Initial feasibility studies were jointly funded and assessed. Recently, there has been a renewed and greatly strengthened effort at regular scientific interchange between these two government agencies. Semiannual meetings on the development of the artificial heart have been held. Through these interactions and the exchange of documents, the Institute has made available to the ERDA recent progress and research information on its devices and technology program. The ERDA, in turn, has made available to the Institute a 33-watt encapsulated plutonium source for conducting important studies on energy sources for artificial hearts.

Hypertension

The effectiveness of treating mild hypertension has not been established. The NHLBI and the VA are sharing the expenses of a pilot clinical trial to determine the feasibility of undertaking a multiyear multicenter double-blind clinical trial on the effectiveness of treating mild hypertension. The full-scale study would attempt to establish whether treatment of mild hypertension results in a reduced incidence of myocardial infarction and/or death from coronary heart disease. The current three-year pilot study underway at four VA hospitals began screening and enrolling participants in July 1974. The study will determine the feasibility of enrolling a sufficient number of participants for a definitive study and will provide an indication of the dropout rate over a one-year period. The pretrial study is scheduled to terminate by June 1977.

NHLBI-VA Propranolol Study

This double-blind study carried out in seven VA hospitals will attempt to determine whether propranolol alone, or with hydrochlorothiazide and/or hydralazine, reduces arterial blood pressure as effectively as the commonly used combination of reserpine and hydrochlorothiazide, and to assess the incidence, severity and gravity of the side effects from treatment with these drugs. The clinical follow-up of this pilot study was completed in December 1976. Analysis of the data is underway and the publication of the results are expected shortly.

Nutrition

The needs of major NHLBI programs such as the Lipid Research Clinics (LRCs) and the Multiple Risk Factor Intervention Trial (MRFIT) for adequate current information on food composition led to a collaborative relationship starting in 1972 between the NHLBI, the US Department of Agriculture (USDA), and the Food

and Drug Administration (FDA). Early accomplishments summarized in previous Reports of the Director of the NHLBI included development and publication of new fatty acid data for all major classes of food, establishment of a Nutrition Coding Center (NCC) to develop and maintain a comprehensive food table and to code all dietary data from the LRCs and the MRFIT, and establishment of a National Nutrition Composition Laboratory (NCL) to consider problems of developing nutrition methodology and of performing food analyses on a routine basis.

The cooperation between the USDA, the FDA, and the NHLBI has been most rewarding. The collaboration has fostered a useful exchange of information and an awareness of each program or agency's needs. The food table maintained at the NCC is perhaps the most current compilation available in terms of reflecting today's food market in the United States. The completeness is particularly apparent in the areas of fatty acid and cholesterol content of foods. The NCL will provide important data not otherwise available for nutritional research.

Direct collaboration among NHLBI nutritionists and other federal agencies ranges from consultation on nutrient composition to participation in epidemiological nutrition survey research. The NHLBI has cooperated with the USDA, the Office of the Assistant Secretary for Health, DHEW, the National Cancer Institute (NCI), and the National Center for Health Statistics (NCHS).

In April 1976, a National Invitational Conference on the Development of Nutrition Data Bases was held under the auspices of the Academy of Pediatrics and the American Dietetic Association. The conference, which included participating nutritionists from the NHLBI and the USDA, reviewed mutual problems and methods of sharing nutrition information among groups working in this area. The conferees felt that the USDA with the help of the NHLBI was making progress in the solution of this problem. Conference recommendations consisted of suggestions as to how the USDA could improve the usefulness of the new nutrition data base from the standpoint of the NHLBI and other users.

Results from NHLBI-sponsored nutrition-behavioral research and other nutritional research have been collated for the Office of the Assistant Secretary for Health, DHEW. This information will be used in a collaborative effort with the North Atlantic Treaty Organization's Committee on the Challenges of a Modern Society.

The NHLBI's Lipid Research Clinic (LRC) Program has entered into a collaborative project involving the Health and Nutrition Examination Survey conducted by the National Center for Health Statistics. The standardized methods of the LRC program will be used to determine serum cholesterol and triglyceride levels in a random national population sample of 4,000 adults per year for three years.

A cooperative activity between the American Diabetes Association, the American Dietetic Association, the National Institute of Arthritis, Metabolism, and Digestive Diseases, and the National Heart, Lung, and Blood Institute has been undertaken to revise and update patient education materials. These materials will be used in the prevention and treatment of diabetics and obesity. They will also be incorporated into the diets developed for reduction of blood lipids in hyperlipidemic patients.

National High Blood Pressure Education Program (NHBPEP)

The NHLBI has the lead responsibility for coordinating the NHBPEP, an interagency and federal/nonfederal cooperative effort. Included in this year's wide range of activities is a joint effort with the NCI to develop a pretest methodology for media messages. In addition, the Institute is working with the FDA on a physician survey and is assisting the NCHS in preparing the report "Health of the Nation"[30] which focuses on hypertension. During the past year, the NHBPEP has been concerned with quality assurance activities in the area of high blood pressure therapy. As a result, a study of five Professional Standards Review Organizations (PSROs) has been developed cooperatively by the NHLBI and the Bureau of Quality Assurance (BQA). A second study involving the BQA, a local PSRO, and a local heart association has also been designed. The Bureau of Community Health Services (BCHS) in the HSA is involving the NHBPEP in a series of regional meetings for their various programs. The program has initiated cooperative activity with the HRA as a result of the National Health Planning and Resources Development Act of 1974 (PL 93-643). The Institute is working with the health systems agencies through the HRA on high blood pressure education planning. For the past several years, the USDA has participated in High Blood Pressure Month through its extension division. Each successive year has seen wider involvement in, and increased comprehensiveness and quality of, reported activities during this special month.

The Community Development Service (CDS) over the past year has initiated contact with 14 states and two multistate councils and continues active involvement with most of these. Documents produced include: the Directory of Community High Blood Pressure Control Activities[31] and the Handbook for Improving High Blood Pressure Control in the Community[32] and a working paper on reducing barriers to health care delivery systems. The CDS is planning and coordinating the National Conference on High Blood Pressure Control. In addition, pamphlets describing how to organize and conduct successful workshops on two specific topics--the pharmacist and high blood pressure control, and community high blood pressure control--have been developed. They will be made available to interested parties during the next year.

Educational materials for physicians have been developed and widely distributed. Guidelines for the Evaluation and Management of the Hypertensive Patient[33] was published under joint sponsorship and distributed by the American Academy of Family Physicians. A similar document was distributed through the Federal Office of Professional Standards Review to their local and support organizations. More recently, an updated set of recommendations in the "Report of the Joint Committee on Detection, Evaluation and Treatment of High Blood Pressure" has been prepared and is scheduled for publication. This document represents the first time a national consensus has been reached among major professional groups on hypertension management. The report of the Working Group on the Training and Evaluation of Physicians was published in Circulation[34] and has also been distributed through the American Association of Medical Colleges and the American College of Preventive Medicine. In addition, the document was supplied to committee members of the National Board of Medical Examiners who prepared questions for the National Boards and Specialty examinations.

The NHBPEP has established a High Blood Pressure Coordinating Committee which is mutually advisory to its participating groups which include the American College of Cardiology, American Medical Association (AMA), American Heart Association (AHA), National Kidney Foundation, Citizens for the Treatment of High Blood Pressure, American Nursing Association, at-large representatives from the public health sector, and the NHLBI. This forum has permitted examination and consensus development on such issues as: approaches to therapy, use of nondrug therapy, improving the precision of blood pressure measurement, purpose and organization of High Blood Pressure Month, annual conduct of a National Conference on High Blood Pressure Control, and other universal interests. The Program also exerts active leadership in a federal working group (a consortium of eight DHEW agencies) for the Training of Physicians in Patient Education. The NHLBI is contributing by developing, in concert with the American Academy of Family Practice and the Association of Teachers of Family Medicine, performance criteria for training family practice residents in patient education.

Diabetes

Diabetes mellitus is a hereditary disease characterized by a variable degree of carbohydrate (sugars and starches) intolerance and specific vascular lesions. Premature atherosclerosis is a major sequela of diabetes, which also leads to changes in both large and small blood vessels of the heart, brain, legs, and retina of the eyes; diabetes can also result in hypertension. As two of the most serious sequelae of this illness, arteriosclerosis and hypertension are major problem areas in the national program; consequently, the NHLBI has a strong commitment to diabetes research and control.

In July of 1974, the National Diabetes Mellitus Research and Education Act was signed into law. The Act called for the establishment of a National Commission on Diabetes to draw up a plan for a coordinated research program in diabetes. Because diabetes-related problems fall within the purview of several NIH Institutes, the directors of these institutes, including the Director of the NHLBI, were appointed to the commission. Ten representatives of the nonfederal sector also serve on this commission which is formulating a long-range plan for a national program of research, education, and treatment of diabetes mellitus. The act also authorized the Diabetes Coordinating Committee, which is chaired by the Director of the NIH and comprised of the same seven NIH Institute Directors as well as representatives from all federal departments and agencies whose programs involve health functions or responsibilities related to diabetes. The Coordinating Committee has adopted definitions of diabetes-related activities under which the participating institutes and agencies can report uniformly those activities that may affect diabetics and diabetes research.

One of the most serious complications of diabetes is diabetic retinopathy. The Diabetes Coordinating Committee is monitoring a study conducted by one of its members, the National Eye Institute. The study involves trials of photocoagulation of small retinal lesions to prevent bleeding into the eye which causes blindness. The treatment has been found effective in delaying blindness, but the length of this delay is uncertain and remains under investigation. The study is being viewed both as a health problem and as a model in coordination which has content and responsibilities of potential applicability to most of the institutes and agencies that participate on the committee.

Smoking and Health

Coordinated research efforts have been continuing over a period of several years in the area of smoking. Cooperative efforts to reduce smoking and to study and detail its harmful effects on health have been conducted by several federal agencies, including the NHLBI, the Center for Disease Control's National Clearinghouse for Smoking and Health, and the Veterans Administration. Studies discussed in previous reports of the Director of the NHLBI have included a smoking withdrawal program which revealed that 70 to 80 percent of the reversals to old habits occur within the first three months following initiation of behavioral change.

An epidemiological study showed that discontinuation of smoking by those who smoke two packs of cigarettes per day results in a gradual reduction of cardiovascular mortality rates to levels approaching those of nonsmokers after about 18 years. For moderate smokers this return to control levels takes at least 10 years.

A pilot NHLBI study demonstrated that baboons can be conditioned to smoke and probably to inhale. Instrumentation has since been refined to measure and analyze the smoking inhalation characteristics of the baboon for comparison with those of man. The smoking baboons will be used to assess the effect of smoking on arteriosclerosis.

The NHLBI is cooperating with the Tobacco Working Group within the NCI. One of the objectives of the NCI program on smoking and health is to develop a less hazardous cigarette for individuals who choose to smoke. The NHLBI is cooperating on a program to bioassay cigarettes that are modified to be less carcinogenic to insure that they are also less pathogenic for chronic lung disease, arteriosclerosis, and heart disease. Modified cigarettes have been developed in the NCI program; carcinogenic activity toward mouse skin is under study and inhalation models for lung cancer are being developed.

Aside from lung cancer, the major pulmonary pathological processes produced by smoking are bronchitis and emphysema. As part of the NIH smoking and health program, the NHLBI supports research to determine which of the currently available tests of pulmonary function will prove most useful in evaluating the effects of smoking in terms of their sensitivity and specificity to acute and chronic responses to cigarette smoke.

Pneumoconiosis (Black Lung)

Because coal miners are at high risk of developing respiratory diseases from exposure to airborne dusts, a joint committee--the Working Party on Respiratory Diseases Among Coal Miners--has been established at the request of the Governor of Pennsylvania to define the types of efforts most urgently required to prevent or treat work-related respiratory diseases. This committee has members from federal (the National Institute for Occupational Safety and Health, the National Institute of Environmental Health Science, the US Bureau of Mines, and the National Heart, Lung, and Blood Institute); state (the Commonwealth of Pennsylvania), nonprofit (the American Lung Association), industry (US Steel and others), and university organizations. Several subcommittees have been organized to evaluate research efforts and to recommend implementation of new activities.

Cystic Fibrosis

Cystic fibrosis is one of the most common genetic diseases that lead to early death. It is characterized by the triad of chronic pulmonary disease, pancreatic exocrine deficiency, and abnormally high sodium and chloride concentration in sweat. A study involving an extensive review of the clinical (but not therapeutic), epidemiologic, historic and pathologic aspects of cystic fibrosis was sponsored jointly by the NHLBI and the NIAMDD and was recently undertaken by the National Academy of Sciences. Three workshops were conducted: (1) cystic fibrosis "factors," (2) prenatal and neonatal screening, and (3) instrumentation for performance of the sweat test. Recommendations for future research were developed for publication.

Emergency Airway Management

Recommended standards for emergency airway maintenance by the lay public and advance life-support personnel (paramedics), and recommendations concerning continuing research and study in this field are the subjects of a program sponsored by the NHLBI and the American Red Cross through the National Academy of Sciences. Recommendations that will be published in the Journal of the American Medical Association in the Spring of 1977 include: (1) causes and factors of airways obstruction, (2) recognition of obstructed airways, (3) effectiveness and complications of current procedures and devices, (4) recommended sequence of their use, (5) methods of application, and (6) how and to whom these devices and procedures will be taught.

Sickle Cell Disease

The NHLBI continues to be actively engaged in cooperative efforts in sickle cell disease. Two interagency sickle cell agreements have been in existence for the past four years. Under the first agreement, twenty-four Screening and Education Clinics are jointly supported in FY 76 by the NHLBI and the HSA. These clinics are functioning in urban, suburban, and rural settings to provide improved public awareness, education, screening, laboratory diagnoses, counseling, and sickle cell patient referral. During the past year, the 25 clinics reached over one million individuals by delivering information and education services to the general public, medical and allied health professionals, employers, and insurers. Screening was provided to more than 600,000 persons and counseling to more than 50,000.

A second interagency sickle cell agreement is with the Center for Disease Control (CDC). The Hematology Division of the CDC is conducting a training program to develop and improve the skills of laboratory technicians in the detection and identification of abnormal hemoglobins with emphasis on sickle hemoglobin. In addition, a proficiency testing program is conducted to upgrade and maintain the quality of work in hemoglobin identification in the federally supported sickle cell projects.

Cooley's Anemia and Hemophilia

In addition to sickle cell disease, the Institute is active in cooperative efforts in the hereditary blood disorders, Cooley's anemia and hemophilia. The NHLBI coordinates its efforts in Cooley's anemia with other NIH components,

the Cooley's Anemia Foundation, and the scientific community. Research programs in this area are discussed with and coordinated through the NIH Interinstitute Coordinating Center on Cooley's Anemia.

The Institute maintains a cooperative working relationship with the National Hemophilia Foundation (NHF). In the past, the NHLBI has jointly sponsored several workshops on problems in hemophilia with the NHF. Current collaborative activities include program planning, information exchange, and research. The foundation has contributed to the development of the National Program--particularly in providing information concerning patient care and contact with the constituency interested in the benefits of hemophilia research.

Hemostasis and Thrombosis (Bleeding and Clotting Disorders)

The NHLBI supports research in the areas of hemostasis and thrombosis and coordinates the efforts of other institutes of the NIH. Close cooperation is maintained with the American Heart Association, especially with the scientific councils that are involved with hemostasis and thrombosis.

The Institute has provided core support to a secretariat of the International Committee on Thrombosis and Hemostasis (ICTH) since 1959. This committee functions on an international scale, forming wide-ranging task forces to attack specific problems. The secretariat coordinates the multiple task forces and the production of their reports. Over the years, the ICTH task forces have been responsible for the introduction of numerous standards such as those used for factor VIII, thrombin, and thromboplastin; for workshops on the standardization of methodologies; for numerous monographs on timely topics; and for the publication of the journal, Thrombosis and Hemostasis.

In March 1975, the NHLBI cosponsored a workshop entitled Animal Models of Thrombosis in Hemorrhagic Diseases. The workshop examined past, present, and future uses and limitations of animal models in research on thrombosis and hemostatis. A major topic of the workshop was recognition maintenance and treatment of these animal models.[35]

Hepatitis

The NIH Viral Hepatitis Coordinating Committee (VHCC) was established in November 1975, replacing the NIH Task Force on Viral Hepatitis Research and the Hepatitis Policy Liaison Committee. The new committee is comprised of representatives from each bureau, institute, or division (BID) of the NIH engaged in any significant way in hepatitis research. The current membership includes the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis, Metabolism, and Digestive Diseases, and the Clinical Center (Blood Bank) of the NIH. The Coordinating Committee has established a liaison relationship with other agencies within the Department of Health, Education, and Welfare, the Department of Defense, and with other government agencies and departments to permit timely and effective exchange of information.

The principal functions of the Coordinating Committee are to channel information and to coordinate all components of the NIH in research on viral hepatitis including the sequelae of infection with hepatitis viruses; to channel

information in these areas between the NIH, other government agencies, and the private sector; and to advise the office of the Director, NIH, on matters related to viral hepatitis.

Blood Research and Blood Resources

The NHLBI's Division of Blood Diseases and Blood Resources has become the focus of coordination with other institutes and with other governmental agencies concerned with research in blood and blood resources. Already, formal as well as informal coordination is taking place, for example, through the Interagency Technical Committee, the NIH Coordinating Committee on Hepatitis, and the newly created formal NIH Coordinating Committee for Blood-Related Activities. This latter committee includes, in addition to the NHLBI, representatives from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Institute for Arthritis, Metabolism, and Digestive Diseases, the National Institute of General Medical Sciences, the National Institute of Child Health and Human Development, the Division of Research Resources, and the Clinical Center Blood Bank.

The Institute plays a role in the continuing implementation of the National Blood Policy, fostering collaboration, coordinating programs, and providing research and development support for joint programs. Participants in these joint programs include other NIH components; the Office of the Secretary of the Department of Health, Education, and Welfare; the Office of the Assistant Secretary of the Department of Health, Education, and Welfare; the Bureau of Biologics of the Food and Drug Administration; and the private sector of the blood banking community.

INTERNATIONAL COLLABORATION

The scientific endeavor recognizes no national borders. Thus, informal exchange of information between scientists in the United States and their peers in other countries has always taken place to the mutual benefit of all. Discussions aimed at producing formal collaborative research agreements are underway with the Federal Republic of Germany (FRG) and Japan. More formal exchanges have taken place between the United States and Egypt as well as with Yugoslavia and several other countries. During the past year, representatives from the FRG Ministry of Research and Technology have met with Institute staff to explore cooperation in artificial circulatory support research, with particular emphasis on biomaterials development, testing, and evaluation. A Joint US-FRG Symposium on Biomaterials Research was held in Munich in June 1976.

The Institute coordinates the US-USSR Health Exchange Program in the cardiovascular area. This program, initiated in 1972, is highly structured and represents a major international collaborative effort of the NHLBI. The goals of the international program are closely related to the goals of the National Program. A second formal US-USSR collaborative program in the area of artificial heart research began in 1974. Both US-USSR agreements call for direct collaboration between United States and Soviet scientists in jointly

planned and executed research activities. Some of the salient activities related to the National Program which are being undertaken under these joint US-USSR agreements are summarized below.

Pathogenesis of Arteriosclerosis

Arteriosclerosis is the most common type of cardiovascular disease and the chief cause of death in both the US and the USSR. Because of the US-USSR agreement, the continent-wide study conducted by the LRCs has been expanded to encompass comparison of the arteriosclerosis problem in the United States and the Soviet Union. This joint clinical study involves large numbers of well-characterized subjects in each country, and by combining data from the US clinics and the USSR clinics, significiantly broader inferences and conclusions will become available. Preliminary biochemical data indicate that there is a significant difference between populations studied in Leningrad and in the US with respect to blood levels of high-density lipoprotein. High levels of this lipoprotein are generally associated with longevity and a decreased risk of heart disease. The data indicate that levels of this lipoprotein in the US population may be lower than those in the population being studied in Leningrad.

Management of Ischemic Heart Disease

Ischemic heart disease is the most common clinical complication of arteriosclerosis and often leads to severe disability or death. This collaborative study is systematically assessing and comparing the treatment of well-characterized heart disease patients in the two countries. The patients in the US-USSR international study will be followed for five years during which period they will be evaluated at least once a year to determine the effectiveness of their respective therapies. The therapies to be evaluated are: "differential" intensive medical management in the USSR, "conventional" medical management in both countries, and coronary artery bypass surgery in the United States. The Third Joint Symposium on Ischemic Heart Disease was held in the USSR in October 1976.

Myocardial Metabolism

A fundamental understanding of the structure and function of the heart muscle is crucial to the development of improved methods of prevention and to therapy of ischemic heart disease. Extensive discussions of many different research projects relating to myocardial metabolism have taken place during joint US-USSR symposia held in 1973 in the US and in 1975 in the USSR. The proceedings of the 1973 Symposium have been published jointly in English and in Russian,[36] and the proceedings of the 1975 symposium are now in press.[37] Particular importance is attached to the participation of young scientists in all phases of this problem area. Joint collaboration has been undertaken in the following areas: studies of protein turnover in the heart, investigations of calcium uptake and release by sarcoplasmic reticulum, studies of cardiac hypertrophy and other compensatory mechanisms, studies of computer simulation of mitochondrial energy transport, and clinical investigation of agents that may restrict the size of myocardial infarction. A Third Joint Symposium on Myocardial Metabolism will be held in the US in May 1977.

Congenital Heart Disease

Congenital heart disease is an important disease of children and young adults both in the United States and in the Soviet Union. Joint US-USSR Symposia on Congential Heart Disease were held in 1973 in the US and in 1975 in the USSR. The proceedings of the first symposium were published jointly in English and in Russian,[38] and the proceedings of the second symposium are in press.[39] Three specific areas have been identified for continued collaboration: problems encountered in congenital heart surgery; clinical symptoms, diagnostic techniques, and surgical treatment of complicated congential heart defects; and postoperative complications of respiration and circulation after open-heart surgery. A third joint symposium will be held in the United States in April 1977.

Sudden Death

Sixty percent of all deaths from coronary heart disease occur before hospitalization. The joint US-USSR efforts on the problem of sudden cardiac death were proposed in 1973, and a series of working meetings of specialists have been held in both countries. Soviet and US investigators are searching together for effective ways to deal with sudden cardiac death. Exchange of information has taken place particularly in the following areas: morphological studies of sudden death, a study of prevalence of cardiac arrhythmias among the population at large, a study of the relationship between cardiac arrhythmias and the risk of sudden death, and emergency services for cardiac arrest victims. Advanced technology for monitoring arrhythmias also has been exchanged. US scientists have collaborated with USSR scientists in organizing a monitoring study to identify subjects at high risk of sudden death in the Sokolniki area of Moscow. The Soviets have shared data on coronary heart disease patients who underwent ambulatory monitoring, and the US has provided data on Multiple Risk Factor Intervention Trial subjects who have been screened for cardiac arrhythmias.

Blood Transfusion, Blood Components, and Prevention of Hepatitis with Particular Reference to Cardiovascular Surgery

Joint US-USSR efforts since 1973 provide for international collaboration in this area of mutual interest. The collaboration of internists and surgeons has been arranged in order to obtain the perspective of both specialties concerning problems of blood management. American and Soviet scientists are exchanging information on important aspects of current blood banking practices in the two countries and are planning further joint efforts to improve the technology and practice of blood transfusion. Two major themes for collaborative scientific investigation have been agreed upon: prevention of hepatitis in blood transfusion; and uses of whole blood, blood components and derivatives, and blood and plasma substitutes. The relationship of both themes to cardiovascular surgery is being emphasized.

Artificial Heart Research and Development

The 1974 US-USSR Agreement in Artificial Heart Research and Development provides for joint research efforts to include the development and testing of cardiovascular support devices, and devices capable of totally replacing a failing heart. In 1974, the NHLBI initiated discussions to develop guidelines for copyright and patent licensing policy to deal with the disposition of rights on any patent which might result from collaborative work in this advanced technology area. English and Russian language agreements of these guidelines were signed by both sides early in 1976. Following the signing of these agreements a reciprocal exchange took place of an implantable US heart and its control mechanisms with a similar Soviet device. Each heart was then implanted by a joint US-USSR team into a calf of the recipient side. These collaborative exchanges of artificial hearts should expedite the development, evaluation, and testing of circulatory assist devices in both countries.

VII.
MANPOWER DEVELOPMENT

Since its inception, the National Institutes of Health (NIH) has been committed to the policy that research training is essential to the development and maintenance of a responsive, high quality national program in both clinical and health-related fundamental research. The success and viability of heart, lung, and blood research efforts will continue to be dependent on the availability of well-trained research scientists and clinicians.

A formidable program of education and training is required of those who seek to carry out clinical investigation and basic scientific research on the frontiers of medical knowledge. The researcher must complete not only an undergraduate program but also must take postgraduate training leading to the MD or PhD. Many professors on medical school faculties have earned both degrees. Beyond the MD and PhD, the young medical scientists must master the ever-increasing complex array of equipment and instrumentation found in the modern laboratory and keep up with the rapidly advancing frontiers of knowledge. Further postdoctoral training under the supervision of teams of senior scientists or physicians in the specialized areas of interest is desirable and is undertaken at considerable personal cost in loss of income; yet great benefit accrues to society in the resultant research and teaching. It is important to attract the most able people into biomedical research and to make it possible for the most promising to obtain the best education and research experience available independent of their own personal resources. It is true that the attrition rate of physicians in research is high; medical practice is both emotionally and financially rewarding, and many times its lure is irresistible. However, a high turnover rate has advantages in that it provides for a continuous stream of new scientists with fresh and innovative ideas into the field of research. A multiplicity of career choices provides avenues for socially productive careers when research creativity may wane.

In all program areas of the Institute there are documented needs to train scientists in many new disciplines to solve complex scientific problems as they arise. Furthermore, the Institute's mandate continues to be increased, and as a result, its programs continue to evolve in greater depth and scope. Newly trained scientists must be available to replace their older colleagues as they retire or move out of research and research teaching into administration or other endeavors.

Table 6 provides a historical tabulation of the National Heart, Lung, and Blood Institute (NHLBI) Manpower Programs. The ten percent decrease in full-time trainees from the peak in 1971 to the present indicates an overall drop in the number of trainees produced under the Institute's mandates. However, the table fails to show the quite significant decrease in personnel training in the cardiovascular field (down over 20 percent since 1970). This absolute decrease is partly hidden by increased numbers of trainees in the lung and blood areas. With the additional lung and blood mandates in FY 72, the Institute assumed the responsibility for support and expansion of both pulmonary and blood manpower programs. During the last few years, several professional societies have assessed the needs for professional manpower in heart, lung, and blood research. The American College of Cardiology, the American Heart Association, the American Association for Thoracic Surgery, the American Thoracic Society, the American College of Chest Physicians, the American Lung Association, the American Society of Hematology, and the American Medical Association have all assessed the training area. Specific requirements have been identified for behavioral scientists; chemists and investigators with specialized training in endocrinology and metabolism experts on blood coagulation; blood banking personnel; individuals with expertise in fundamental nutrition, lipid metabolism, growth and development, and pediatrics; epidemiologists and biostatisticians. Currently, there is an exceptional need for nutritionists and epidemiologists to fill vacancies in important new programs which have evolved in response to the 1972 National Heart, Blood Vessel, Lung and Blood Act. These include the Centers Programs, the Clinical Trials Programs, and Prevention, Education and Control Programs.

The NHBLI has responded to such surveys as this and those of the National Research Council and the National Academy of Sciences by placing high priority on increasing the number of both individual and institutional National Research Service Awards.

The general prospect for the next few years is a rising demand for new entrants into heart, lung, and blood disease research training. In relation to this, the NHLBI training funds requested for FY 78 and beyond will meet only a small portion of the probable need.*

HEART AND VASCULAR DISEASES

Tentative but conservative estimates indicate that 400 to 500 new beginning investigators must enter postdoctoral training each year to maintain current

*See under *Activities Related to the National Program*, p. 36.

research manpower for heart and vascular diseases alone. Some 1,000 additional trained persons appear necessary to fill identified medical school vacancies. In addition to these general needs, specific needs for behavioral scientists, population geneticists, epidemiologists, biostatisticians, nutritionists, hypertension investigators, microcirculationists, protein and immunochemists, endocrinologists, metabolic experts, coagulation experts, and pathologists total approximately 800 new investigators required to implement the expanded activities of the National Plan.

LUNG DISEASES

The report of an ad hoc committee to survey Pulmonary Disease Manpower conducted at the request of the American Thoracic Society in 1972 states:

> "...as has been documented convincingly by the results of this survey, there is a serious discrepancy between the number of chest physicians currently being trained, and the number of chest physicians needed now and desired in the future."[40]

At present, there are not enough physicians and scientists available to meet identified lung research needs. The Institute estimates a need for approximately 280 new training positions in FY 77. This shortage of qualified professionals retards both the application of available knowledge and the acquisition of new knowledge pertaining to lung diseases. Hence, a major goal of the manpower program is to support lung-related training of medical school faculty members, both clinicians and basic scientists. The underlying determinants of pulmonary physiology and pathology are being investigated to an increasing extent. Such investigations require training in fundamental disciplines which only recently have been applied to lung research. Therefore, pulmonary physicians and basic scientists must be encouraged to collaborate in interdisciplinary approaches to solve pulmonary problems of mutual concern. Clinical respiratory disease training programs for internists and pediatricians must also be provided. These programs also place special emphasis on formal interdisciplinary training.

BLOOD DISEASES

Since the fields of hematology and blood banking have come to encompass widely divergent and specialized areas of expertise, future training programs should recognize the need for specialization while at the same time provide the breadth and depth of biological experience essential for new innovative approaches. Thus, new kinds of professionals are needed in blood research in addition to those required to fill vacancies in traditional areas. An accurate accounting of personnel availability and needs must be developed for both blood diseases and blood resources. Pressing training needs have been identified in the blood banking sciences. Because of the rapid evolution and complexity of blood banks, an increase is planned in the training of postdoctoral research scientists in this field. The current 7 to 8 graduates per year must be increased to over 25. In addition, there is a shortage of qualified directors for blood banks and

transfusion facilities. Skilled professionals are needed to deal with thromboembolic and hemorrhagic complications arising in connection with vascular prostheses, renal dialysis and transplant, and cardiac support units as well as in many other situations. Training in thrombosis and hemostasis also needs to be expanded.

RESEARCH TRAINING AWARDS

The National Research Service Award (NRSA) Act of 1974 repealed all previous training authorities of the NHLBI. Therefore, in accordance with this legislation all previous fellowship and traineeship programs are being phased out. However, 665 persons were still in training under such programs in FY 76. Under the NRSA legislation, the NHLBI may make both individual and institutional training awards in areas of specified shortage and relevance to its programs. The NHLBI places great emphasis on postdoctoral training because this type of training can supply the multidisciplinary personnel required to carry out its program.

The National Research Service Awards (NRSA) for Individual Postdoctoral Fellows

This new award, first made in FY 75 and used throughout the Institute, supports Postdoctoral Fellows in specified areas of biomedical and behavioral research in which a documented need for trained manpower exists. In FY 75, 138 such awards were made. This increased to 193 awards in FY 76, and the Institute hopes to increase individual Postdoctoral Fellowship Awards to at least 250 awards annually by FY 78.

The National Research Service Awards for Institutional Research Training (NRSA Institutional)

This award is given to eligible institutions to develop or enhance research training opportunities for individuals selected by the institutions who are interested in careers in specified areas of biomedical and behavioral research. The NHLBI employs these institutional awards to foster the development of highly trained individuals in the fields where needs are not adequately met by the Individual Fellowship Awards. The Institute funded 71 National Research Service Awards for institutional research training during FY 75 which supported 57 predoctoral and 222 postdoctoral trainees in several areas of acute need. In FY 76, a total of 106 Institutional Research Service Awards were funded; these supported 101 predoctoral candidates and 390 postdoctoral trainees.

RESEARCH PROGRAMS EMPHASIZING SCIENTIFIC MANPOWER DEVELOPMENT

Innovative manpower development programs are being pursued in relation to the new and unique NHLBI missions defined by recent legislation. These progams are planned and tailored to specific requirements and opportunities. As a result, some of the NHLBI manpower development programs are considered as research activities rather than as training programs and are supported by research funds.

Minority Hypertension Research Development Summer Program

In response to the identified need for minority investigators in problems related to hypertension, a program to provide summer research experience for minority school faculty and graduate students will be initiated in FY 77. This program will communicate knowledge of opportunities and required research skills to minority individuals within their own institutional settings.

Minority Biomedical Research Support Program

This program, sponsored by the NIH Division of Research Resources, is designed to encourage research participation by minority school students. In keeping with NIH policy, the NHLBI is participating financially in this program, and has identified and is funding portions of program projects: 16 elements in the area of heart and vascular diseases, 4 elements in the area of lung diseases, and 5 elements in the area of blood diseases and blood resources.

National Pulmonary Faculty Training Program

This program includes several interlocking components designed to strengthen pulmonary faculties at schools of medicine and osteopathy and to enhance their training environment. Junior faculty members from schools wishing to strengthen their pulmonary academic programs can obtain specialized pulmonary training at medical centers where the training environment is supported through the National Faculty Training Program. In 1975, six training centers were selected, and the initial review of applications for trainee positions was conducted. In FY 76, ten junior faculty numbers were selected to take part in this program.

Pulmonary Academic Award (PAA) Program

The PAA Program was initiated in 1971 to foster a stimulating approach to respiratory disease curricula, to ensure superior modern instruction in respiratory diseases, to attract the interest of medical students to respiratory medicine, to help the careers of teacher-investigators, and to encourage schools to recognize respiratory diseases as a subspecialty. To date, there are 30 PAAs in medical schools in the United States. The original goal of the program was to establish a PAA in each school of medicine and osteopathy in this country.

Young Investigator Research Grant Program

A Young Investigator Research Grant Program was introduced in the pulmonary area in 1974. As a result of the initial success of this program in attracting well qualified individuals into the area of respiration research, the Institute expanded the program in FY 76 to include the heart and vascular, and blood areas. The purposes of this program are to encourage research in fundamental as well as clinical disciplines, to enable young scientists and physicians to explore their developing research interests, and to provide young investigators with modest support for a project of their own design. Thus, this program provides a mechanism for research funding during the

interval between completion of a fellowship and qualification for a Research Career Development Award--an interval when support is usually difficult to obtain. To date, 75 Young Investigator Research Grants have been awarded in the pulmonary area, and increasing numbers of applications are being received. The success and value of the program have attracted considerable interest, and the program is serving as a model for similar programs now being developed by other Institutes at the NIH.

Research Career Development Award (RCDA) Program

The RCDA program is Institute-wide, and its aim is to support individuals with outstanding research potential who require additional training and experience in a productive scientific environment in preparation for a career in independent research. This ongoing program provides an important mechanism of long-term five-year funding for promising young scientists. Since 1970, approximately 132 individuals per year have been supported by this mechanism. Of these, 52 percent were in the cardiovascular area, 23 percent in lung research, and 20 percent in blood-related endeavors.

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